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4

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Signed Andrew Gerry

Dated 4 September 2000

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THE PATENT OFFICE K -7 OCT 1999 LONDON

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your Reference — **MJS/DMK/PI3806**

2. Pa (Th — **9923748.9** — **7 OCT 1999**

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its corporation — **GB**

6735870 03

4 Title of the invention — **CHEMICAL COMPOUNDS**

5 Name of your agent *(if you know one)* — **MICHAEL J STOTT (SEE CONTINUATION SHEET)**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXO WELLCOME PLC
GLAXO WELLCOME HOUSE, BERKELEY AVENUE
GREENFORD, MIDDLESEX
UB6 ONN, GB

Patents ADP number *(if you know it)* 13575750 03

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

YES

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9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	1
Description	61
Claim(s)	3
Abstract	2
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature MICHAEL J STOTT 07 October 1999
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

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0181-966 8685

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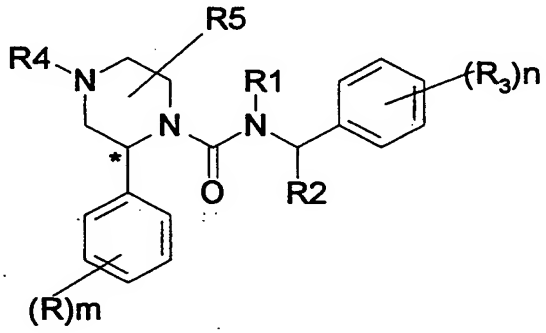
Chemical Compounds

The present invention relates to piperazine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to novel compounds which are potent and specific antagonists of tachykinins, including substance P and other neurokinins.

The present invention provides compounds of formula (I)



(I)

wherein

R represents a halogen atom or a C_{1-4} alkyl group;

R_1 represents hydrogen or a C_{1-4} alkyl group;

R_2 represents hydrogen or a C_{1-4} alkyl group;

R_3 represents a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, a trifluoromethoxy or a halogen group;

R_4 represents hydrogen, a $(CH_2)qR_7$ or a $(CH_2)rCO(CH_2)pR_7$ group;

R_5 represents hydrogen, a C_{1-4} alkyl or a COR_6 group;

R_6 represents hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R_7 represents hydrogen, hydroxy, a saturated 5-7 membered heterocyclic group, a 5 member d heteroaryl group containing 1 to 3 heteroatoms s l cted from oxygen, sulphur and nitrogen, a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or NR_8R_9 wherein R_8

and R_9 represent independently hydrogen or C_{1-4} alkyl optionally substituted by a hydroxy, amino, by a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, by a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or saturated 5-7 membered heterocyclic or R_8 and R_9 together with the nitrogen atom to which they are attached represent a saturated 5-7 membered heterocyclic group optionally containing an additional heteroatom selected from oxygen, sulphur or nitrogen;
m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; p or r are zero or an integer from 1 to 4; q is an integer from 1 to 4 and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least one chiral centre (namely the carbon atom shown as * in formula (I).
Thus, when R_2 is a C_{1-4} alkyl or a trifluoromethyl group and R_5 is hydrogen, the compounds of formula (I) possess two asymmetric carbon atoms. Furthermore, when R_2 is a C_{1-4} alkyl or a trifluomethyl group and R_5 is a C_{1-4} alkyl or a COR_6 group, the compounds of the invention possess three asymmetric carbon atoms. It is to be understood that all enantiomers and diastereomers and mixtures thereof are encompassed within the scop of the present invention.

The term alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, or tert butyl.

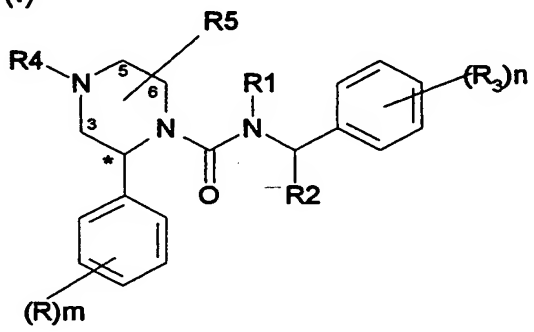
The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term C_{1-4} alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, pro-2-oxy, butoxy, but-2-oxy or methylpro-2-oxy.

When R_6 or R_7 are a 5 or 6 membered heteroaryl group or when R_8 or R_9 are C_{1-4} alkyl optionally substituted by a 5 or 6 membered heteroaryl group, according to the invention they include furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridyl or pyrimidinyl.

When R_7 is a saturated 5-7 membered heterocyclic group or when R_8 or R_9 are C_{1-4} alkyl optionally substituted by a 5-7 membered heterocyclic group, this may be for example morpholino, 2,6 dimethylmorpholino, thiomorpholino, piperidyl, pyrrolidinyl, piperazinyl or N-methylpiperazinyl.

The group R_5 may be in position 3, 5 or 6 of the piperazine ring of compounds of formula (I)



(I)

When R represents halogen this is suitably chlorine or more preferably fluorine or when R is C_{1-4} alkyl this is suitably methyl or ethyl wherein m is 0 or an integer from 1 to 2.

Suitable values for R_1 or R_2 include hydrogen, a methyl, an ethyl or a propyl group.

R_1 and R_2 are suitably both hydrogen or suitably both a methyl group or suitably one of the R_1 and R_2 is a methyl group and the other is hydrogen.

Suitable values for R_3 include a methyl, an ethyl or a trifluoromethyl group.

When R_4 is (CH2)qR7 or (CH2)rCO(CH2)pR7, R_7 is suitably a hydrogen, hydroxy, furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridyl, morpholino, piperidinyl, pyrrolidinyl, NR_9R_8 e.g. NH2, NH(C_{1-4} alkyl) e.g. NH methyl or N(C_{1-4} alkyl)$_2$ e.g. N(methyl)$_2$, NH(C_{1-4} alkyl)NH_2 e.g. NH(ethyl)NH_2, NH(C_{1-4} alkyl)morpholino or NH(C_{1-4} alkyl) pyridyl wherein q is 1 or 2 and p or r are zero or an integer from 1 to 2.

Suitable values for R_5 include hydrogen, a C_{1-4} alkyl (e.g. methyl) group, $CONH_2$or $CONHCH_3$.

R is preferably a halogen (e.g. fluorine) and /or a C_{1-4} alkyl (e.g. methyl) group and m is preferably zero or an integer from 1 to 2.

R_1 is preferably a hydrogen atom or a methyl group.

R_2 is preferably a hydrogen atom or a methyl group.

R_3 is preferably a trifluoromethyl group.

R_4 is preferably a hydrogen atom, an amino C_{1-4} alkyl(e.g. aminoethyl) group, aminoacetyl, amino(C_{1-4}alkyl)aminocarbonyl, morpholino(C_{1-4}alkyl aminocarbonyl), pyridyl C_{1-4} alkylamino carbonyl, piperidylcarbonyl.

R_5 is preferably a hydrogen atom or a methyl group.

A preferred class of compounds of formula (I) are those wherein R is a halogen (e.g. fluorine) and /or a C_{1-4} alkyl (e.g. methyl) group, wherein m

is 0,1 or 2. More preferably m is 2. Within this class those wherein R is at the 2 and 4 position are particularly preferred.

Compounds of formula (I) wherein R_3 is a trifluoromethyl group and n is 2 represent a preferred class of compounds and within this class R_3 is preferably at the 3 and 5 position.

Also a preferred class of compounds of formula (I) are those wherein R_1 or R_2 represent independently hydrogen or a methyl group, R_4 is hydrogen and R_5 is hydrogen or a methyl group.

A further preferred class of compounds of formula (I) are those wherein R_1 or R_2 represent independently hydrogen or a methyl group, R_4 is hydrogen and R_5 is hydrogen.

A further preferred class of compounds of formula (I) are those wherein R_4 is a $(CH_2)rCO(CH_2)pR_7$ group, wherein R_7 represents an amine group or a piperidinyl group or R_4 is a $(CH_2)qR_7$ group wherein R_7 is an amine group. Within this class, those wherein p or r are zero or 1 or q is 1 or 2 are particularly preferred.

A particularly preferred group of compounds of formula (I) is that R is halogen and/or methyl, R_3 is trifluoromethyl at the 3 and 5 position, R_1 and R_2 are independently hydrogen or methyl, R_4 is hydrogen, an aminoacetyl piperidinecarbonyl or amino ethyl group and R_5 is hydrogen or a methyl group.

A further particularly preferred group of compounds of formula (I) is that R is halogen and/or methyl, R_3 is trifluoromethyl at the 3 and 5 position, R_1 and R_2 are independently hydrogen or methyl, R_4 is hydrogen and R_5 is hydrogen.

Suitable compounds according to the invention are:
2-(3-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;
(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

and pharmaceutically acceptable salts and solvates thereof.

Preferred compounds according to the invention are:

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

2-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;;

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;

2-(4-Fluoro-phenyl)- piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide;

2-Phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl- amide;

2-(2,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;

2-(3,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide;

2-(4-Fluoro-2-methyl-phenyl)-3-methyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

2-(2-Methyl-4-Fluoro-phenyl)-6-Methyl- piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide;

and pharmaceutically acceptable salts and solvates thereof.

Particularly preferred compounds according to the invention are:

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (mixture of enantiomers A/B);

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (mixture of enantiomers C/D); 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (enantiomer A); 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; (enantiomer C); and pharmaceutically acceptable salts and solvates thereof; 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; acetate salt (enantiomer C); 4-(2-Amino-acetyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, and pharmaceutically acceptable salts and solvates thereof; 4-(2-Amino-acetyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride

The compounds of the invention are antagonists of tachykinins, including substance P and other neurokinins both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

The compounds of the invention possess NK_1-receptor binding affinity as determined in vitro by their ability to displace [3H]- substance P (SP) from NK_1 receptors in cell membranes of U-373MG human astrocytoma cells. U-373MG membranes (25-35μg protein per tube) were prepared and incubated with [3H]-SP (0.6-0.8nM) at 20°C for 40min. Non-specific binding was defined as that remaining in the presence of 1μM (+) CP-99,994.

NK_1-receptor binding affinity has been determined in vitro by the compounds' ability to displace [3H] - substance P (SP) from recombinant human NK_1 receptors expressed in Chinese Hamster Ovary (CHO) cell membranes.

CHO cell membranes were prepared by using a modification of the method described by Dam T and Quirion R (Peptides, 7:855-864, 1986). Thus ligand binding was performed in 0.4 ml of 50 mM HEPES, pH 7.4, containing 3 mM $MnCl_2$, 0.02% BSA, 0.5 nM [^{3}H]Substance P (30÷56 Ci/mmol, Amersham), a final m mbran concentration of 25 μg of

protein/ml, and the test compounds. The incubation proceeded at room temperature for 40 min. Non-specific binding was determined using excess of Substance P (1 μM) and represents about 6% of the total binding.

Compounds of invention were further characterised in a functional assay for the determination of their inhibitory effect. Human-NK_1-CHO cells were stimulated with Substance P and the receptor activation was evaluated by measuring the accumulation of cytidinediphosphodiacylglycerol (CDP-DAG), which is the liponucleotide precursor of phosphatidylinositol diphosphate. CDP-DAG accumulates in the presence of Li^+ as a consequence of the receptor mediated activation of phospholipase C (PLC) (Godfrey, Biochem. J., 258:621-624, 1989). The method is described in detail by Ferraguti et al. (Mol. Cell. Neurosci., 5:269-276, 1994).

The action of the compounds of the invention at the NK_1 receptor may be determined by using conventional test. Thus the ability to bind at the NK_1 receptor was determined using the gerbil foot tapping model as described by Rupniak & Williams, Eur. Jur. of Pharmacol., 1994.

Compounds of the invention have also been found to exhibit anxiolytic activity in conventional tests. For example in marmoset human threat test (Costall et al., 1988).

Compounds of the invention may be useful in the treatment of CNS disorders in particular in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedativ s, hypnotics, anxiolytics and other substances;

schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disord rs r lated to immun enhancement or

suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

The compounds of the invention are of particular use in the treatment of depressive states, in the treatment of anxiety and of panic disorders. Depressive states include major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, dysthymic disorder with early or late onset and with or without atypical features, neurotic depression and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the all viation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but

the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

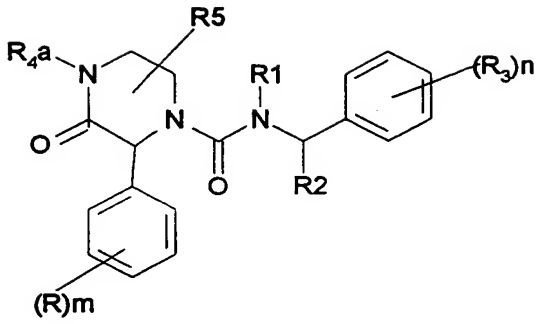
The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1, R_2, R_4, R_5, m, n, p, q and r have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

According to general process (A), a compound of formula (I) wherein R_4 is hydrogen or a $(CH_2)qR_7$ group as defined in formula (I), provided that when R_5 is a C_{1-4} alkyl or a COR_6 group, R_5 is not in 3 position of the piperazine ring, may be prepared by reduction of a ketopiperazine of formula (II), wherein R_{4a} is hydrogen or a suitable nitrogen protecting group or R_{4a} is a $(CH_2)qR_7$ group or protecting derivatives thereof followed where necessary or desired by removal of any protecting group.

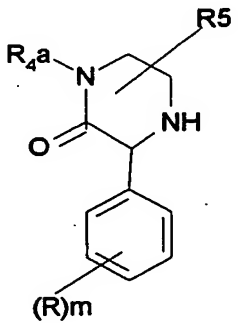


(II)

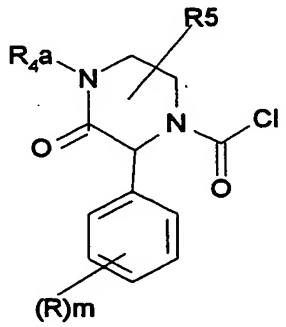
The reaction may be carried out using a suitable metal reducing agent such as a metal hydride, for example a borane hydride, alane hydride or a metal hydride complex like lithium aluminum hydride or sodium borohydride, or an organo-metallic complex such as borane- methyl sulphide, 9-borabicyclononane (9-BBN), triethylsilane, sodium triacetoxyborohydride, sodium cyanoborohydride.

Suitable solvents for this reaction are ether (e.g tetrahydrofuran), or halohydrocarbon (e.g. dichloromethane) or an amide (e.g. N,N-dimethylformamide) at a temperature within the range of room temperature to the reflux temperature of the reaction mixture.

Compounds of formula (II) may be prepared by treating compounds of formula (III) wherein R_{4a} and R_5 have the meaning defined in formula (II)

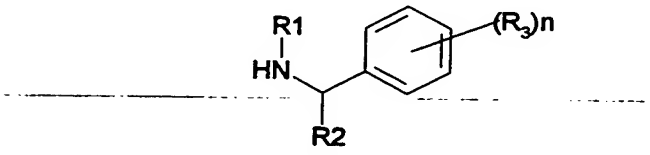


(III)



(IV)

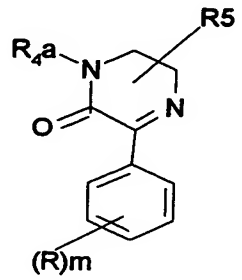
with triphosgene in aprotic solvent such as dichloromethane and in the presence of an organic base such triethylamine to form the intermediate carbonyl chloride compound (IV) which may be isolated if required, followed by reaction of compound (IV) with the amine compound (V)



(V)

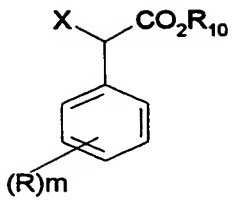
The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon, a halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran optionally in the presence of a base such as a tertiary amine e.g. diisopropyl ethyl amine.

Compounds of formula (III) are either known compounds or may be prepared by analogous method. Thus for example a compound of formula (III) may be prepared by reduction of a dihydropyrazin-2-one (VI) using a suitable metal reducing agent such as sodium borohydride. Alternatively, catalytic hydrogenation may be used, for example using Palladium on Carbon catalyst in a suitable solvent such as methanol.



(VI)

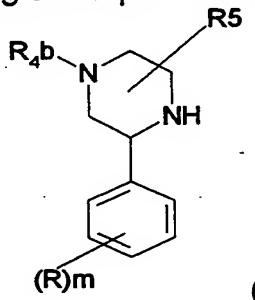
Alternatively compounds of formula (III) wherein R_5 is hydrogen may be prepared by reaction of compounds of formula (VII), wherein R_{10} is a C_{1-4} alkyl group and X is a suitable leaving group such as halogen, i.e. bromine or iodine atom, or OSO_2CF_3,



(VII)

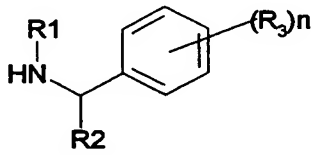
with ethylendiamine. The reaction conveniently takes place in a suitable solvent such as alcohol (i.e. ethanol) at an elevated temperature.

According to a further general process (B) a compound of formula (I) wherein R_4 is hydrogen or $(CH_2)rCO(CH_2)p\ R_7$ as above defined may be prepared by reacting a compound of formula (VIII),



(VIII)

wherein R_{4b} represents a nitrogen protecting group or R_{4b} is $(CH_2)r\ CO(CH_2)pR_7$ or a protecting group thereof, with triphosgene in an aprotic solvent such as dichloromethane and in the presence of an organic base such triethylamine to form the intermediate carbonyl chloride compound (IV) which may be isolated if required, followed by reaction of compound (IV) with the amine compound (V)



(V)

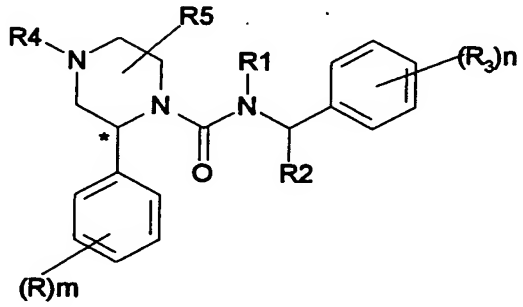
The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon, a halohydrocarbon such as dichloromethane or an ether

such as tetrahydrofuran optionally in the presence of a base such as a tertiary amine e.g. diisopropyl ethyl amine, followed by deprotection where necessary.

When R_{4a} or R_{4b} is nitrogen protecting group examples of suitable groups include alkoxycarbonyl e.g. t-butoxycarbonyl, benzyloxycarbonyl,arylsulphonyl e.g. phenysulphonyl or 2-trimethylsilylethoxymethyl.

Protection and deprotection may be effected using conventional techniques such as those described in "Protective Groups in Organic Synthesis 2nd Ed." by T.W. Greene and P. G. M. Wuts (John Wiley and Sons, 1991) and as described in the examples hereinafter.

Compounds of formula (I) wherein R_4 is a $CO(CH_2)pR_7$ group or protective derivatives thereof may be also prepared by reaction of the compound of formula (I)



(I)

wherein R_4 is a hydrogen atom, with an activated derivative of the acid $R_7(CH_2)pCO_2H$(IX).

The activated derivatives of the carboxylic acid (IX) may be prepared by conventional means. Suitable activated derivatives of the carboxylic group include the corresponding acyl halide, mixed anhydride, activated ester such as thioester or the derivative formed between the carboxylic acid group and a coupling agent such as that used in peptide chemistry, for example carbonyl diimidazole or a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

The reaction is preferably carried out in an aprotic solvent such as an amide e.g. N,N-dimethylformamide or acetonitrile.

Compounds of formula (I) wherein R_4 is $CONR_9R_8$in which R_9 or R_8 have the meaning defined in formula (I) may be prepared by reaction of a compound of formula (I) wherein R_4 is a hydrogen atom with triphosgene in an aprotic solvent such as dichloromethane and in the presence of an organic base such as triethylamine followed by reaction with the amine compound $NR_9R_8(X)$.

Alternatively compounds of formula (I) wherein R_4 is a $CONHR_9$ group in which R_9 is C_{1-4} alkyl may be also prepared by reaction with isocyanate of formula $R_9NC=O$ (XI). The reaction with the compound (XI) is conveniently carried out in a solvent such as tetrahydrofuran or aqueous tetrahydrofuran, a halohydrocarbon (e.g. dichloromethane) or acetonitrile optionally in the presence of a base such as triethylamine and at temperature within the range 0-80°C.

In a further embodiment compounds of formula (I) wherein R_4 is $(CH_2)qR_7$ or R_4 is $(CH_2)rCO(CH_2)pR_7$ wherein q, r and R_7 have the meanings defined in formula (I) or are protective derivatives thereof with the provision that r is not zero, may also be prepared by reaction of compounds of formula (I) wherein R_4 is a hydrogen group with a compound of formula (XII) $R_7(CH_2)qX$ or $X(CH_2)rCO(CH_2)pR_7$ (XIII), in which X is a leaving group such as halogen e.g. chlorine, a bromine atom, a mesyl or a tosyl group.

In a further preferred embodiment compounds of formula (I) wherein R_4 is $(CH_2)qR_7$ wherein q and R_7 have the meanings defined in formula (I) or are protective derivatives thereof may be also prepared by reaction of compounds of formula (I) wherein R_4 is a hydrogen group with a compound of formula (XIV) $R_7(CH_2)qCHO$ (XIV), in which q is zero or an integer from 1 to 3 and R_7 has the meanings defined in formula (I) or are protective derivatives thereof, in the presence of suitable metal reducting agent such as $NaCNBH_3$.

Where it is desired to isolate a compound formula (I) as a salt, for example a pharmaceutically acceptable salt, this may be achieved by reacting th compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an

alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether or tetrahydrofuran).

Compounds of formula (VI) and (VIII) are known compounds or may be prepared by analogous methods to those used for known compounds.

Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.

Thus specific enantiomers of the compounds of formula (I) in which R_4 is an hydrogen atom may be prepared by reaction of a suitable chiral alcohol, in the presence of a source of a carbonyl group (such as triphosgene or carbonyl diimidazole) separating the resultant diastereoisomeric carbamates by conventional means e.g. chromatography or by fractional crystallisation. The required enantiomer of a compound of general formula (I) may be isolated by removal of carbamate and conversion into the required free base or salts thereof.

Suitable chiral alcohol for use in the process include (*R*)-*sec*-phenylethyl alcohol, etc.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Thus for example the required enantiomer may be prepared by the corresponding enantiomeric amine of formula (III) using any of the processes described above for preparing compounds of formula (I) from th amine (III). The enantiomer of amine (III) may be prepar d from the

racemic amine (III) using conventional procedures such as salt formation with a suitable optically active acid such as L(+)mandelic acid.

The invention is further illustrated by the following Intermediates and Examples which are not intended as a limitation of the invention.

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refers to °C. Infrared spectra were measured on a FT-IR instrument. Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me_4Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m). Column chromathography was carried out over silica gel (Merck AG Darmstaadt, Germany). The following abbreviations are used in text: EA = ethyl acetate, CH = cyclohexane, DCM = dichloromethane, THF = tetrahydrofuran, TFA = trifluoroacetic acid, TEA = triethylamine, PPA = polyphosphoric acid, DBU = 1,8-diazobicyclo [5,4,0]undec-7-ene, DMSO = dimethylsulphoxide, IMS=mixture of Ethanol with 5% of methanol,LHDMS=Lithiumbis(trimethylsilyl)amide DIPEA=diisopropylethylamine Tlc refers to thin layer chromatography on silica plates, and dried refers to a solution dried over anhydrous sodium sulphate; r.t. (RT) refers to room temperature.
Enantiomer A or enantiomer B refer to a single enantiomer whose absolute stereochemistry was not characterised.

Intermediate 1

2-Methyl-4-fluoroboronic acid

To magnesium turnings (0.5g), heated at 90°C, a solution of commercial 2-bromo-5-fluorotoluene (2ml) in THF (3ml) was added drop-wise. The reaction mixture was heated at 90-95°C for 1 ½ hr, and then the mixture was diluted with other THF (10ml) and transferred in a dropping funnel. The latter solution and trimethylborate (2.1ml) were simultaneously added to stirred diethyl ther (15ml), maintaining the temperatur below -60°C. The reaction mixture was allow d to warm to r.t., then the stirring

was continued for 1 ½ hr. Water (6ml) was added and the reaction mixture was stirred overnight. Ethyl acetate was added and the solution was washed with 1N HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product which was triturated in diethyl ether/petroleum (25ml/75ml) to obtain the title compound as a trimer (1.44g, white powder).
NMR (DMSO) δ (ppm) 7.87 (m, 3H), 6.99-6.93 (m, 6H), 2.6 (s, 9H)

Intermediate 2

2-(4-fluoro-2-methyl-phenyl)-pyrazine.

A mixture of intermediate 1 (1.34g), 2-chloropyrazine (1ml) and bis[1,2-bis(diphenylphosphino)ethane]-palladium(0) (0.21g) in toluene/1M sol. Na_2CO_3 /EtOH95% 20ml/20ml/10ml was heated at reflux for 2 hr. The solution was poured into ethyl acetate and washed with brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography to obtain the title compound (1.4g) as a white powder.
m.p.=66-68°C
NMR (DMSO) δ (ppm) 8.81 (d, 1H), 8.72 (m, 1H), 8.63 (d, 1H), 7.52 (m, 1H), 7.22 (m, 1H), 7.17 (m, 1H), 2.35 (s, 3H).

Intermediate 3

2-(3-Isopropyl-phenyl)-pyrazine

To a solution of commercial 3-isopropyl-benzene boronic acid (1.0g) in a 2:2:1 mixture of toluene/1M Na_2CO_3/EtOH (122 mL), at r.t.,2-chloropyrazine (599 µL) and the bis[1,2-bis(diphenylphosphino)ethane]-palladium(0) catalyst (110mg) were added. The reaction mixture was heated at 80°C for 3 hr. It was then cooled down and partitioned between EtOAc/sat.aq. NaCl. The phases were separated and the organic layer was dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a clear oil (468 mg).
NMR ($CDCl_3$): δ (ppm) 9.02 (d, 1H), 8.63 (m, 1H), 8.49 (d, 1H), 7.89 (m, 1H), 7.80 (m, 1H), 7.44 (t, 1H), 7.35 (d, 1H), 3.02 (m, 1H), 1.31 (d, 6H).

Intermediate 4

2-(2-Isopropyl-phenyl)-pyrazine

1) To a suspension of magnesium turnings (134 mg) in anh. THF (2.5 mL), at r.t., under N_2, a small crystal of I_2 was added, followed by 10% of a solution of commercial 1-bromo-2-isopropyl-benzene (1.0 g) in anh. THF (2.6 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 60°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

2) To a solution of the 2-chloropyrazine (448 µL) in anh. THF (5.1 mL), at 0°C, under N_2, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (100mg) and the Grignard solution were successively added drop-wise. The brown solution was stirred at r.t. for 30 min, then at reflux for 3 hr. It was then poured in sat.aq. NaCl/CH_2Cl_2 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography obtaining the title compound as a yellow oil (676 mg).

NMR ($CDCl_3$): δ (ppm) 8.67 (d, 1H), 8.67 (m, 1H), 8.54 (d, 1H), 7.5-7.3 (m, 4H), 3.13 (m, 1H), 1.20 (d, 6H).

Intermediate 5

2-(4-Fluoro-3-methyl-phenyl)-pyrazine

1) To a suspension of magnesium turnings (167 mg) in anh. THF (2.6 mL), at r.t., under N_2, a small crystal of I_2 was added, followed by 10% of a solution of commercial 4-bromo-1-fluoro-2-methyl-benzene (1.0g) in anh. THF (2.7 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 60°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

2) To a solution of the 2-chloropyrazine (472 µL) in anh. THF (5.3 mL), at 0°C, under N_2, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (100mg) and the Grignard solution were successively added drop-wise.

The brown solution was stirred at r.t. for 30 min, then at reflux for 3 hr. It was then poured in sat.aq. NaCl/CH_2Cl_2 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography. The title compound was obtained as a yellow oil (571mg).

NMR ($CDCl_3$): δ (ppm) 8.98 (d, 1H), 8.60 (m, 1H), 8.49 (d, 1H), 7.87 (m, 1H), 7.80 (m, 1H), 7.13 (t, 1H), 2.37 (s, 3H).

Intermediate 6

2-(2,4-Difluoro-phenyl)-pyrazine

1) To a suspension of magnesium turnings (139 mg) in anh. THF (2.6 mL), at r.t., under N_2, a small crystal of I_2 was added, followed by 10% of a solution of commercial 1-bromo-2,4-difluoro-benzene (1.0 g) in anh. THF (2.6 mL). The suspension was heated gently (heat gun) until the brown-colour disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 60°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

2) To a solution of the 2-chloropyrazine (463 µL) in anh. THF (5.2 mL), at 0°C, under N_2, [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (50mg) and the Grignard solution were successively added drop-wise. The brown solution was stirred at r.t. for 30 min, then at reflux for 3 hr. It was then poured in sat.aq. NaCl/CH_2Cl_2 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography. The title compound was obtained as a yellow solid (175mg).

NMR ($CDCl_3$): δ (ppm) 9.01 (dd, 1H), 8.78 (dd, 1H), 8.66 (d, 1H), 7.99 (td, 1H), 7.47 (td, 1H), 7.29 (td, 1H).

Intermediate 7

2-(4-fluoro-2-methyl-phenyl)-piperazin hydrochloride.

A two n ck round bottom flask was equipped with a water condenser and a dropping funnel and was flushed with N_2. Mg turnings (1.45g) were introduced in the flask and were suspended in anh. THF (5 mL). A small crystal of I_2 was added in order to activate the Mg. The dropping funnel was filled with a solution of the commercial 2-bromo-5-fluorotoluene (10g) in anh. THF (30 mL). The solution of the bromide was added drop-wise to the Mg turnings and the solution warmed up to approximately 70°C. The solution was kept at that temperature until the complete disappearance of the Mg turnings.

Meanwhile, 2-chloropyrazine (4.75 mL) was dissolved in anh. THF (30 mL) and [1,2-bis(diphenylphosphino)ethane]dichloronickel(II) (510mg) was added. To this suspension the solution of Grignard was added drop-wise, at 0°C, under N_2. After the addition was complete, the reaction mixture was heated at reflux for 2 hr. The THF was evaporated, the residue poured in sat. aq. NaCl and the aqueous phase was extracted with CH_2Cl_2 (3x). The organic extracts were dried over Na_2SO_4, the solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography and then through a small column of Florisil (eluant: CH_2Cl_2) to eliminate the nickel residue (6.0 g). 2-(4-fluoro-2-methyl-phenyl)-pyrazine (6.0 g) was obtained as a pale yellow solid.

2-(4-fluoro-2-methyl-phenyl)-pyrazine (0.3g) dissolved in EtOH 95% (20ml) and 37% HCl (0.2ml) was hydrogenated at 5 atm. for 4hr, in the presence of 20% $Pd(OH)_2/C$ (30mg) as catalyst. The catalyst was filtered off and the solvent was evaporated. The crude residue was triturated in MeOH/AcOEt (5ml/15ml) to obtain the title compound (0.08g) as a white powder.

m.p. >220 °C

NMR (DMSO) δ (ppm) 9.72 (broad, 2H), 7.90 (d, 1H), 7.21-7.17 (m, 2H), 4.85 (m, 1H), 3.57-3.2 (m, 6H), 2.40 (s, 3H).

Intermediate 8

3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 7 (0.25g) and triethylamine (0.5ml) in CH_2Cl_2 (15ml) a solution of benzylchloroformate (0.15ml) in CH_2Cl_2

(10ml) was added drop-wise, at 0°C. The reaction mixture was stirred at 0°C for 2hr, then washed with brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography to obtain the title compound (0.21g) as a colourless oil.

NMR ($CDCl_3$, 40°C) δ (ppm) 7.52 (m, 1H), 7.4-7.3 (m, 5H), 6.9-6.8 (m, 2H), 5.16 (dd, 2H), 4.12 (m, 2H), 3.86 (m, 1H); 3.3-2.7 (m, 4H), 2.33, (bs, 3H).

Intermediate 9

3-(3-Isopropyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 3 (428 mg) in anh. EtOH (47 mL), at r.t., under N_2, conc. HCl (492 µL) and $Pd(OH)_2/C$ 20% (86 mg, 20% wt) were added. The black suspension was placed in a PARR apparatus and the hydrogenation was done at r.t. under 7 atm of H_2 for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. The filtrate was evaporated to dryness. The grey solid 2-(3-Isopropyl-phenyl)-piperazine hydrochloride (654 mg) was dissolved in anh. CH_2Cl_2 (24 mL), at 0°C, under N_2, then triethylamine (1.32 mL) and benzylchloroformate (404 µL) were added. The solution was stirred at 0°C for 2 ½ hr. It was then poured in CH_2Cl_2/sat.aq. NaCl/sat.aq. K_2CO_3 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a yellow oil (192mg).

NMR ($CDCl_3$): δ (ppm) 7.34-7.12 (m, 8H), 5.08 (m, 2H), 3.89 (bd, 1H), 3.85 (bm, 1H), 3.55 (bd, 1H), 3.0-2.65 (bm, 6H), 1.17 (d, 6H).

Intermediate 10

3-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid benzyl ester.

To a solution of intermediate 4 (315mg) in anh. EtOH (40 mL), at r.t., under N_2, conc. HCl (529 µL) and $Pd(OH)_2/C$ 20% (63mg, 20% wt) were added. The black suspension was placed in a PARR apparatus and the hydrogenation was done at r.t. und r 7 atm of H_2 for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. Th filtrate was vaporated to dryness. The grey solid 2-(2-Isopropyl-phenyl)-

piperazine hydrochloride (411mg) was dissolved in anh. CH_2Cl_2 (16 mL), at 0°C, under N_2, then triethylamine (886 µL) and benzylchloroformate (272 µL) were added. The solution was stirred at 0°C for 2.5 hr. It was then poured in CH_2Cl_2/sat.aq. NaCl/sat.aq. K_2CO_3 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a yellow oil (117mg).
NMR ($CDCl_3$): δ (ppm) 7.52 (d, 1H), 7.4-7.3 (m, 5H), 7.26 (d, 1H), 7.21 (t, 1H), 7.14 (t, 1H), 5.14 (d, 1H), 5.03 (d, 1H), 4.0-3.8 (m, 3H), 3.23 (m, 1H), 2.99 (m, 1H), 2.91 (m, 1H), 2.8-2.0 (m, 2H), 1.19 (d, 6H).

Intermediate 11
3-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 5 (314mg) in anh. EtOH (30 mL), at r.t., under N_2, conc. HCl (350 µL) and $Pd(OH)_2$/C 20% (30mg, 10% wt) were added. The black suspension was placed in a PARR apparatus and the hydrogenation was done at r.t. under 7 atm of H_2 for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. The filtrate was evaporated to dryness. The grey solid 2-(4-Fluoro-3-methyl-phenyl)-piperazine hydrochloride (411mg) was dissolved in anh. CH_2Cl_2 (15 mL), at 0°C, under N_2, then triethylamine (858 µL) and benzylchloroformate (264 µL) were added. The solution was stirred at 0°C for 2.5 hr. It was then poured in CH_2Cl_2/sat.aq. NaCl/sat.aq. K_2CO_3 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a yellow oil (170mg).
NMR ($CDCl_3$): δ (ppm) 7.3-7.4 (m, 5H), 7.23 (m, 1H), 7.17 (m, 1H), 6.96 (t, 1H), 5.17 (m, 2H), 4.15 (m, 2H), 3.67 (m, 1H), 2.7-3.2 (m, 4H), 2.27 (s, 3H).

Intermediate 12
3-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 6 (175mg) in anh. EtOH (30 mL), at r.t., under N_2, conc. HCl (228 µL, 2.5 eq) and $Pd(OH)_2/C$ 20% (20mg, 10% wt) were added. The black suspension was placed in a PARR apparatus and the hydrogenation was done at r.t. under 7 atm of H_2 for 18 hr. The catalyst was then filtered on Celite and the Celite cake rinsed with MeOH. The filtrate was evaporated to dryness. The greenish solid 2-(2,4-Difluoro-phenyl)- piperazine hydrochloride (247mg) was dissolved in anh. CH_2Cl_2 (9.1 mL), at 0°C, under N_2, then triethylamine (508 µL) and benzylchloroformate (162 µL) were added. The solution was stirred at 0°C for 3 hr. It was then poured in CH_2Cl_2/sat.aq. NaCl/sat.aq. K_2CO_3 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography obtaining the title compound as a yellow oil (100mg).

NMR ($CDCl_3$): δ (ppm) 7.49 (m, 1H), 7.3-7.4 (m, 5H), 6.76-6.8 (m, 2H), 5.16 (s, 2H), 4.15 (m, 2H), 4.03 (m, 1H), 2.8-3.15 (m, 4H).

Intermediate 13

4-[(3,5-bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester.

To a solution of intermediate 8 (0.05g) and triethylamine (0.15ml) in CH_2Cl_2 (10ml), a solution of triphosgene (0.02ml) in CH_2Cl_2 (10ml) was added drop-wise, at 0°C. The reaction mixture was allowed to warm to r.t. in 3hr, then diisopropylethylamine (0.07ml) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (53mg) were added. The reaction mixture was stirred at reflux for 2hr and at r.t. overnight, then was washed with a 1N solution of HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product, which was purified by flash column chromatography to obtain the title compound (0.05g) as a colourless oil.

NMR ($CDCl_3$) δ (ppm) 7.76 (s, 1H), 7.49 (s, 2H), 7.4-7.3 (m, 5H), 7.20 (dd, 1H), 6.86 (d, 1H), 6.79 (m, 1H), 5.17 (s, 2H), 4.66 (d, 1H), 4.64 (m, 1H), 4.36 (d, 1H), 3.97 (m, 2H), 3.4 (m, 2H), 3.16 (m, 2H), 2.93 (s, 3H), 2.38 (bs, 3H).

Int rmediat 14

4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(3-isopropyl-phenyl)piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 9 (192 mg) in anh. CH_2Cl_2 (7 mL), at 0°C, under N_2, triethylamine (237 µL) was added. To this solution a solution of triphosgene (76mg) in anh. CH_2Cl_2 (4 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr.

To this solution diisopropylethylamine (198 µL) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (200 mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2, washed with 10% citric acid (1x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a thick oil (353 mg).

NMR ($CDCl_3$): δ (ppm) 7.91 (bs, 1H), 7.84 (bs 2H), 7.36-7.26 (m, 5H), 7.18-7.10 (m, 2H), 7.06 (m, 2H), 5.07 (s, 2H), 4.76 (t, 1H), 4.50 (bs, 2H), 3.96 (dd, 1H), 3.66 (td, 1H), 3.57 (dd, 1H), 3.4-3.3 (m, 2H), 3.19 (m, 1H), 2.86 (s, 3H), 2.76 (m, 1H), 1.09 (2d, 6H).

Intermediate 15

4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(2-isopropyl-phenyl)-piperazine-1-carboxylic acid benzyl ester.

To a solution of intermediate 10 (46 mg) in anh. CH_2Cl_2 (3.9 mL), at 0°C, under N_2, triethylamine (145 µL) was added. To this solution a solution of triphosgene (46 mg) in anh. CH_2Cl_2 (3 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr.

To this solution diisopropylethylamine (121 µL) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (122 mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2, washed with 10% citric acid (1x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a clear oil (108 mg).

NMR ($CDCl_3$): δ (ppm) 7.89 (bs, 1H), 7.71 (bs, 2H), 7.38-7.28 (m, 5H), 7.28 (dd, 1H), 7.23 (dd, 1H), 7.16 (dt, 1H), 7.01 (dt, 1H), 5.14 (d, 1H), 5.05 (bd, 1H), 4.68 (dd, 1H), 4.52 (2d(AB), 2H), 3.83 (dd, 1H), 3.71 (dt,

1H), 3.53 (md, 1H), 3.41 (dt, 1H), 3.26 (m, 1H), 3.15-3.05 (m, 2H), 1.19 (d, 3H), 1.13 (m, 3H).

Intermediate 16

4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(4-fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 11 (170 mg) in anh. CH_2Cl_2 (7 mL), at 0°C, under N_2, triethylamine (217 µL) was added. To this solution a solution of triphosgene (69 mg) in anh. CH_2Cl_2 (3 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr.

To this solution diisopropylethylamine (181 µL) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (183 mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2, washed with 10% citric acid (1x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a gummy solid (226mg).

NMR ($CDCl_3$): δ (ppm) 7.77 (m, 1H), 7.60 (m, 2H), 7.3-7.4 (m, 5H), 7.05-7.15 (m, 2H), 6.90 (m, 1H), 5.14 (m, 2H), 4.6-4.8 (m, 1H), 4.54 + 4.47 (AB, 2H), 3.82 (bm, 1H), 3.73 (dd, 1H), 3.65 (m, 1H), 3.57 (m, 1H), 3.33 (m, 1H), 3.26 (m, 1H), 2.90 (s, 3H), 2.19 (s, 3H).

Intermediate 17

4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(2,4-difluoro-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 12 (95 mg) in anh. CH_2Cl_2 (3 mL), at 0°C, under N_2, triethylamine (120 µL) was added. To this solution a solution of triphosgene (38mg) in anh. CH_2Cl_2 (3 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr.

To this solution diisopropylethylamine (100 µL, 2 eq) and (3,5-bis-trifluoromethyl-benzyl)-methyl-amine hydrochloride (101mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2, washed with 10% citric acid (1x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crud oil was purified by flash chromatography. The title compound was obtained as a yellow gum (134mg).

NMR ($CDCl_3$): δ (ppm) 7.76 (s, 1H), 7.56 (s, 2H), 7.26-7.40 (m, 6H), 6.76 (m, 2H), 5.17 (m, 2H), 4.83 (m, 1H), 4.36-4.60 (dd + m, 2H), 3.90 (m, 1H), 3.25-3.7 (m, 2H), 2.86 (s, 3H).

Intermediate 18

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 8 (0.15g) and triethylamine (0.32ml) in CH_2Cl_2 (35ml), a solution of triphosgene (0.065ml) in CH_2Cl_2 (25ml) was added drop-wise at 0° C. The reaction mixture was allowed to warm to r.t. in 3 hr, then pyridine (0.3ml) and 3,5-bis(trifluoromethyl)benzyl-1-methyl-amine hydrochloride (53mg) were added. The reaction mixture was stirred at r.t. overnight, then washed with a 1N solution of HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography to obtain the title compound (0.086g) as a pale yellow oil and 4-benzyloxycarbonyl-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carbonyl chloride (0.075g).

Title compound: NMR ($CDCl_3$) δ (ppm) .78-7.7 (m, 1H), 7.5-7.4 (m, 2H), 7.4-7.25 (m, 5H), 7.20 (m, 1H), 6.95-6.8 (m, 2H), 5.2-5.05 (m, 2H), 4.99 (dd, 1H), 4.6-4.2 (m, 2H), 4.5-4.15 (m, 2H), 3.8-3.6 (m, 2H), 4.12 (m, 1/2H), 3.91 (m, 1/2H), 3.61 (m, 1/2H), 3.44 (m, 1/2H), 2.4-2.2 (s+s, 3H).

Intermediate 19

3-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester

To a solution of 1,1'carbonyldiimidazole (0.162g) in CH_2Cl_2 (5ml) (S)-sec-Phenethyl alcohol (0.122g) was added. After 30 min. a solution of intermediate 7 (0.180g) in CH_3CN (5ml) was added and the mixture refluxed for 2 hr. Then the mixture was concentrated to give the crude product which was purified by flash chromatography (cyclohexane ethyl acetate 80: 20) to obtain the title compound (mix diastereomer) (0.180g) as a foam.

NMR (DMSO) δ (ppm) 7.87 (m, 1H); 7.40-7.25 (m, 5H); 7.02-6.94 (m, 2H); 5.74 (m, 1H); 3.93-3.71 (m, 3H); 3.00-2.55 (m, 4H); 2.34 (s, 3H); 2.28 (s, 3H)

Intermediate 20

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereomer 1) (20a)

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereomer 2) (20b)

To a solution of intermediate 19 (0.180g) and triethylamine (0.35ml) in CH_2Cl_2 (5 ml) a solution of triphosgene (0.075g) in CH_2Cl_2 (5ml) was added drop-wise at 0° C. After 2 hr, diisopropylethylamine (0.3ml) and (3,5-bistrifluoromethylbenzyl)-methyl-amine hydrochloride (0.209g) were added and the mixture was warmed at r.t. After 4 hr CH_2Cl_2 was added and the organic phase was washed with HCl 1N (2 x 10ml) and brine, dried with Na_2SO_4 and concentrated to give the crude diastereisomeric mixture. Separation by flash chromatography (silica gel, 8:2 cHex/EtOAc) yielded the title compound 20a (0.125g) and the title compound 20b (0.135g) as white foams.

Intermediate 20a NMR (DMSO) δ (ppm) 7.90 (s, 1H); 7.67 (s, 2H); 7.4-7.27 (m, 6H); 6.95 (dd, 1H); 6.80 (m, 1H); 5,74 (q, 1H); 4.60-4.40 (dd, 2H); 4.50 (m, 1H); 3.79 (m, 3H); 3.00 (m, 3H); 2.87 (s, 3H); 2.29 (s, 3H); 1.46 (d, 3H).

Intermediate 20b NMR (DMSO) δ (ppm) 7.90 (s, 1H); 7.67 (s, 2H); 7.37-7.24 (m, 6H); 6.95 (dd, 1H); 6.81 (m, 1H); 5.75 (q, 1H); 4.60-4.41 (dd, 2H); 4.52 (m, 1H); 3.83-3.00 (m, 6H); 2.88 (s, 3H); 2.33 (s, 3H); 1.48 (d, 3H).

Intermediate 21

[1-(2,4-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine

To a 2 M solution of $MeNH_2$ in MeOH (10 ml) commercial 3,5-Bis(trifluoromethyl)acetophenone (2.1g) was added. After 12 hr the mixture was cooled at 0° C and then $NaBH_4$ (0.512g) was added. After 1 hr the mixture was quenched with H_2O and extracted with CH_2Cl_2. Then the organic phase was dried with Na_2SO_4 and concentrated to give the crude product which was purifi d by distillation to obtain the title compound (1.5g) as an oil.

NMR ($CDCl_3$) δ (ppm) 7.8 (m, 3H); 3.8 (q, 1H); 2.4 (s, 3H); 1.4 (d, 3H)

Intermediate 22
4-{[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester (mixture of enantiomers AB) (22a)
4-{[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid benzyl ester (mixture of enantiomers C,D)(22b)

To a solution of 4-benzyloxycarbonyl -2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carbonyl chloride (0.075g) in CH_2Cl_2 (5 ml) diisopropylethylamine (0.12ml) and intermediate 21 (0.1g) were added. The mixture was refluxed for 2 hr, then CH_3CN (5ml) was added and the obtained solution was heated 70° C and the mixture was stirred overnight. Then the mixture was concentrated and the residue was dissolved in ethylacetate. The organic phase was washed with HCl 1N and brine and dried with Na_2SO_4. Then the organic phase was concentrated to give the crude mixture of diastereomeric compounds which were separated by flash chromatography (silica gel, 8:2 cHex/EtOAc) to obtain intermediate 22a (0.05g) and intermediate 22b (0.55g) as white foams.

Intermediate 22a NMR ($CDCl_3$) δ (ppm) 7.78 (s, 1H); 7.58 (s, 2H); 7.4-7.3 (m, 5H); 7.18 (m, 1H); 6.86 (m, 1H); 6.77 (m, 1H); 5.45 (m, 1H); 5.16 (s, 2H); 4.6 (m, 1H); 3.94 (m, 2H); 3.44-3.10 (m, 4H); 2.68 (s, 3H); 2.4 (s, 3H); 1.49 (d, 3H).

Intermediate 22b NMR ($CDCl_3$) δ (ppm) 7.75 (s, 1H); 7.53 (s, 2H); 7.4-7.3 (m, 5H); 7.18 (m, 1H); 6.87 (m, 1H); 6.78 (m, 1H); 5.59 (m, 1H); 5.18 (s, 2H); 4.59 (m, 1H); 3.97 (m, 2H); 3.44-3.06 (m, 4H); 2.78 (s, 3H); 2.37 (s, 3H); 1.53 (d, 3H).

Intermediate 23
(4-Fluoro-2-methyl-phenyl)-oxo-acetic acid methyl ester

1) To a suspension of magnesium turnings (617 mg) in anh. THF (6 mL), at r.t., under N_2, a small crystal of I_2 was added, followed by a solution of commercial 2-bromo-5-fluorotoluen (4.0g) in anh. THF (15 mL). Th susp nsion was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise,

maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 70°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.

2) A solution of LiBr (4.41 g) in anh. THF (50 mL) was added drop-wise to a suspension of CuBr (3.64g) in anh. THF (50 mL). The reaction mixture was stirred at r.t. for 1 hr (dark green solution with a small amount of white solid in suspension). The Grignard solution prepared above was then added drop-wise (an ice bath was used to maintain the temperature <25°C) followed by methyl oxalyl chloride (1.95 mL). The reaction mixture was stirred at r.t. for 2 hr. The THF was evaporated and the residue was taken up in EtOAc. The organic layer was washed with sat.aq. NH_4Cl (2x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated to give a crude oil, which was purified by flash chromatography to obtain the title compound as a clear oil (2.44g).
NMR ($CDCl_3$): δ (ppm) 7.74 (m, 1H), 6.98-7.04 (m, 2H), 3.96 (s, 3H), 2.61 (s, 3H).

Intemediate 24

(4-Fluoro phenyl)-oxo- acetic acid methyl ester

To magnesium turnings (0.066 g), previously heated at 90 °C and covered by THF (1ml), a crystal of iodine was added followed by a solution of commercial 4-Fluoro-bromobenzene (0.437g) in THF (4ml). The temperature was kept at 60°C till the consumption of the metal. The solution of the organometallic derivative was added drop-wise on a solution of CuBr (0.356 g) and LiBr (0.431g) in THF (10ml), previously prepared at 0°C.
At the end of the addition methyl oxalyl chloride (0.225ml) was added via syringe and the reaction mixture was stirred 2h at r.t, before being poured into an aqueous saturated solution of NH_4Cl and extracted with Et_2O. The organic phase was washed with brine and dried on Na_2SO_4. The crude product obtained after evaporation of solvents was purified by column chromatography affording the title compound (0.2g) as a solid.
^{1}H-NMR ($CDCl_3$): δ (ppm): 8.12 (m, 2H), 7.20 (m, 2H), 3.99 (s, 3H).

Int rmediat 25

3-(4-Flu ro-2-methyl-phenyl)-5,6-dihydro-1H-pyrazin-2-on

To a solution of intermediate 23 (2.01g) and ethylene diamine (684 μL) in toluene (40 mL), at r.t., under N_2, anh. Na_2SO_4 (2g) was added. The reaction mixture was heated at reflux for 6 hr. It was then cooled down to r.t. and filtered. The solids were rinsed with CH_2Cl_2. The solvent was evaporated and the crude oil was purified by flash chromatography affording the title compound as a white solid (1.29g).
NMR ($CDCl_3$): δ (ppm) 7.33 (m, 1H), 6.95-6.90 (m, 2H), 6.56 (m, 1H), 3.97 (m, 2H), 3.58 (m, 2H), 2.31 (s, 3H).

Intermediate 26

3-(4-Fluoro-phenyl)-5,6 dihydro-1H-pyrazin-2-one

Intermediate 24 (0.190g) was dissolved in dry toluene (5ml) under inert atmosphere; ethylendiammine (0.072ml) was added drop-wise followed by Na_2SO_4 (0.2g) and the reaction mixture was refluxed 2 hr. The solids were filtered off and the crude product obtained after evaporation of the solvent was purified by flash chromatography affording the title compound (0.155g as a white solid).

mp 118-120°C

^{1}H-NMR ($CDCl_3$) δ (ppm): 7.96 (m, 2H), 7.08 (m, 2H), (bs, 1H), 3.96 (t, 2H), 3.54 (m, 2H).

Intermediate 27

Bromo-(2,4-dicholoro-phenyl)-acetic acid methyl ester.

To a stirred solution of commercial 2,4-dichlorophenylacetic acid (2g) in CH_2Cl_2 (50ml) DMF (0.1ml) and oxalyl chloride (1.7ml) were added and the reaction mixture was heated at reflux for 1 ½ hr. The solvent was evaporated and the crude compound was dissolved in carbon tetrachloride (40ml). N-bromosucinimide (1.8g) and 2,2'-azobis(2-methylpropionitrile) (0.1g) were added and the reaction mixture was heated at reflux and irradiated for 2 hr. After cooling, methanol (50ml) was added and the reaction mixture was stirred for 1 hr. The solution was concentrated, diluted with ehtyl acetate and washed with a ^{3}N HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to obtain a mixture of the title compound and 2,4-dichlorophenyl-acetic acid, m thyl ester (1.3g).

This mixture was dissolved in carbon tetrachloride (20ml) then N-bromosucinimide (0.89g) and 2,2'-azobis(2-methylpropionitrile) (0.05g) were added and the reaction mixture was heated at reflux and irradiated for 3 ½ hr. The solution was concentrated, diluted with ehtyl acetate and washed with a saturated solution of Na_2CO_3 and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to yield the title compound (1.14g, pale yellow oil).

NMR ($CDCl_3$): δ (ppm) 7.72 (d, 1H), 7.40 (d, 1H), 7.30 (dd, 1H), 5.84 (s, 1H), 3.81 (s, 3H)

Intermediate 28

Bromo-(3,4-dicholoro-phenyl)-acetic acid methyl ester.

To a stirred solution of commercial 3,4-dichlorophenylacetic acid (2g) in CH_2Cl_2 (100 ml) DMF (0.1ml) and oxalyl chloride (1.7ml) were added and the reaction mixture was heated at reflux for 1 ½ hr. After cooling, methanol (50ml) was added and the reaction mixture was stirred for 1 hr. The solvent was evaporated and the crude compound was purified by flash column chromatography to obtain the methyl ester that was dissolved in carbon tetrachloride (60ml). N-bromosucinimide (2.06g) and 2,2'-azobis(2-methylpropionitrile) (0.2g) were added and the reaction mixture was heated at reflux and irradiated for 2hr. The solution was concentrated, diluted with ethyl acetate and washed with a saturated solution of Na_2CO_3 and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to obtain the title compound (2.0g) as an oil.

NMR ($CDCl_3$) δ (ppm) 7.70 (s,1H), 7.45 (m,1H), 5.25 (s, 1H), 3.80 (s, 3H)

Intermediate 29

3-(2,4-dichloro-phenyl)-piperazine-2-one.

To a solution of intermediate 27 (1.14g) in EtOH (20ml) sodium ethoxide (0.34g) and ethylenediamine (0.54ml) were added and the reaction mixture was stirred at r.t. for 15 hr. The solvent was evaporated and the residue was purifi d by flash column chromatography to yield the titl compound (0.35g, whit foam).

NMR (DMSO): δ (ppm) 7.87 (broad, 1H), 7.55 (d, 1H), 7.41, 7.37 (d+dd, 2H), 4.63 (s, 1H), 3.32, 3.14 (m+m, 2H), 3.02-2.90, 2.84 (m+m, 3H).

Intermediate 30

3-(3,4-dichloro-phenyl)-piperazine-2-one.

To a solution of intermediate 28 (2.0g) in EtOH (100ml) sodium ethoxide (0.60g) and ethylenediamine (0.95ml) were added and the reaction mixture was stirred at r.t. for 15 hr. The solvent was evaporated and the residue was diluted with ethyl acetate and washed with brine. The organic phase was next dried with Na_2SO_4 and concentrated to give a crude residue which was purified by flash column chromatography to yield the title compound (2.0g, white foam).

NMR ($CDCl_3$): δ (ppm) 7.60 (d, 1H), 7.42 (d, 1H), 7.32, (dd, 1H), 5.91 (sa, 1H), 4.53 (s, 1H), 3.6-3.1 (m+m, 4H).

Intermediate 31

3-Oxo-2-phenyl-piperazine-1-carbonyl chloride

To a stirred solution of triphosgene (0.558g) in CH_2Cl_2 (10ml) pyridine (0.46ml) was added at 0°C and, after 10 min, 3-phenyl-piperazine-2-one (1g). The ice bath was removed and the mixture was stirred at room temperature overnight. The mixture was concentrated and the product was purified by flash chromatography to give the title compound (0.253g) as a foam.

NMR ($CDCl_3$): δ(ppm): 7.45-7.35 (m, 5H); 6.81 (bs, 1H); 6.61 (bs, 1H); 5.99 (s, 1H); 4.3-4.2 (m, 1H); 3.7-3.3 (m, 3H)

Intermediate 32

2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of intermediate 25 (63mg) in anh. CH_3OH (6.1 mL), at r.t., under N_2, Pd/C 10% (7 mg, 10% wt) was added. The reaction mixture was placed under an H_2 atmosphere and was stirred at r.t. for 2 hr. The catalyst was filtered (filtering paper) and the solvent was evaporated. The crude 3-(4-Fluoro-2-methyl-phenyl)-piperazin-2-one (64mg) was dried under high vacuum and dissolved in anh. CH_2Cl_2 (4.0 mL), at 0°C, under N_2, and Et_3N (85 μL) was added. To this solution, a solution of

triphosgene (37 mg) in anh. CH_2Cl_2 (2 mL) was added drop-wise. The reaction was stirred at 0°C for 2 hr. To this solution iPr_2NEt (107 µL) and N-methyl-bis(trifluoromethyl)-benzylamine hydrochloride (108 mg) were added. The solution was stirred at r.t. for 18 hr. The reaction mixture was diluted with CH_2Cl_2, washed with 1N HCl (1x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography. The title compound was obtained as a white solid (93mg).

NMR ($CDCl_3$): δ (ppm) 7.79 (s, 1H), 7.59 (s, 2H), 7.20 (bs, 1H), 6.91-6.84 (m, 1H), 6.07 (m, 1H), 5.69 (s, 1H), 4.58-4.47 (dd, 1H), 3.49 (m, 4H), 2.85-2.39 (s, 6H).

Intermediate 33

2-(4-Fluoro-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide

Intermediate 26 (0.135g) was dissolved in CH_3OH (5ml) and the temperature lowered at 0°C, then $NaBH_4$ (0.102g) was carefully added. After 2 hr the reduction was complete, the solvent was removed under reduced pressure and CH_2Cl_2 was added. The organic phase was washed with H_2O and brine before being dried on Na_2SO_4. The crude 3-(4-Fluoro-phenyl)-piperazin-2-one (0.140g) was dried under high vacuum and dissolved in anhydrous CH_2Cl_2 (5ml), at 0°C and triethylamine (0.433ml) was added drop-wise. To this solution a solution of triphosgene (0.09g) in dry CH_2Cl_2 (3ml) was added at 0°C, under inert atmosphere. The temperature was maintained at 0°C for 3 hr, then diisopropylethylamine (0.4ml) followed by 3,5-bistrifluoromethyl-methyl-amine hydrochloride (0.27g) were added. The reaction mixture was stirred at r.t. overnight before being diluted with CH_2Cl_2 and washed with a 1N solution of HCl, H_2O and brine in sequence. The organic phase was dried on Na_2SO_4 and the crude product obtained after evaporation of the solvent was purified by flash column chromatography affording the title compound as a foam (0.2g).

NMR (DMSO): δ (ppm) 8.14 (bs, 1H), 7.97 (s, 1H), 7.78 (s, 2H), 7.37 (2H, m), 7.09 (m, 2H), 5.13 (s, 1H), 4.49 (dd, 2H), 3.5-3.25 (4H, m), 2.80 (3H, s).

Intermediate 34

3-Oxo-2-phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a stirred solution of intermediate 31 (0.239g) in DMF (5ml) diisopropylethylamine (0.41ml) and 3,5-bistrifluoromethyl-methyl-amine hydrochloride (0.366g) were added. After 3 hr the mixture was quenched with brine and the aqueous layer was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. The product was purified by flash chromatography to give the title compound (0.429g).

NMR ($CDCl_3$): δ (ppm): 7.79(bs, 1H); 7.67(bs, 2H); 7.50(d, 2H); 7.35(m, 3H); 5.98(s, 1H); 5.43(s, 1H): 4.63-4.32(dd, 2H); 3.88-3.56(m, 2H); 3.50-3.30(m, 2H); 2.81(s, 3H);.

Intermediate 35

2-(2,4-dichloro-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

To a solution of intermediate 29 (0.33g) in CH_2Cl_2 (30ml) triethylamine (0.65ml) and, drop-wise, a solution of triphosgene (0.23g) in CH_2Cl_2 (10ml) were added. The reaction mixture was stirred at r.t. for 1 ½ hr then concentrated and purified by flash column chromatography to yield 2-(2,4-dichloro-phenyl)-3-oxo-piperazine-1-carbonyl chloride (0.3g, white foam). The latter was dissolved in CH_2Cl_2 (30ml), then diisopropylethylamine (0.3ml) and (3,5-bistrifluoromethylbenzyl)-methyl-amine hydrochloride (0.32g) were added. The reaction mixture was stirred at reflux for 3 hr, then washed with a 1N solution of HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography to obtain the title compound (0.45g, white foam).

NMR (DMSO) δ (ppm) 8.30 (bs, 1H), 7.96 (bs, 1H), 7.73 (bs, 1H), 7.54 (d, 1H), 7.35, 7.33 (d+dd, 2H), 5.44 (s, 1H), 4.61 (d, 1H), 4.39 (d, 1H), 3.39, 3.25 (m+m, 4H), 2.76 (s, 3H).

Intermediate 36

2-(3,4-dichloro-phenyl)-3-oxo-pip razin -1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.

To a solution intermediate 30 (0.413g) in CH_2Cl_2 (40ml) triethylamine (1.4ml) and, drop-wise, a solution of triphosgene (0.25g) in CH_2Cl_2 (10ml) was added. The reaction mixture was stirred at r.t. for 1 ½ hr, then diisopropylethylamine (0.6ml) and (3,5-bistrifluoromethylbenzyl)-methyl-amine hydrochloride (0.54g) were added. The reaction mixture was stirred at reflux for 3hr, then washed with a 1N solution of HCl and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product which was purified by flash column chromatography to obtain the title compound (0.13g, white foam).

NMR (DMSO) δ (ppm) 8.24 (bs, 1H), 7.96 (s, 1H), 7.75 (s, 2H), 7.54 (d, 1H), 7.51(d,1H), 7.33 (dd, 1H), 5.11 (s, 1H), 4.49 (dd, 2H), 3.5- 3.25 (m+m, 4H), 2.82 (s, 3H).

Intermediate 37

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(R)-phenyl-ethyl ester (diastereomer 1) (37a)

4-(3,5-bis-trifluoromethyl-benzyl-carbamoyl)-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(R)-phenyl-ethyl ester (diastereomer 2) (37b)

To a solution of carbonyl diimidazole (402mg) in CH_2Cl_2 (8.3ml), at r.t., under N_2, (*R*)-*sec*-phenylethyl alcohol (0.3 mL) was added. The solution was stirred at r.t. for 1 hr. Example 11(790mg) in anh. CH_3CN (8.3 mL) was then added to the solution and the reaction mixture was heated at 50°C without a water condenser in order to evaporate the CH_2Cl_2. A water condenser was then adjusted to the flask and the reaction mixture was refluxed for 4 hr. The solvent was then evaporated and the residue partitioned between EtOAc/1N HCl. The phases were separated and the organic layer was washed with sat. aq. NaCl (2x). It was then dried over Na_2SO_4, the solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography (silica gel, 8:2 cHex/EtOAc). The mixed fractions were re-chromatographed using the same conditions. Intermediates 37a (242 mg) and 37b (152mg) were obtained as white foams.

Intermediat 37a

NMR (DMSO) δ (ppm): 7.90 (s, 1H); 7.67 (s, 2H); 7.37-7.24 (m, 6H); 6.95 (dd, 1H); 6.81 (m, 1H); 5.75 (q, 1H); 4.60-4.41 (dd, 2H); 4.52 (m, 1H); 3.83-3.00 (m, 6H); 2.88 (s, 3H); 2.33 (s, 3H); 1.48 (d, 3H).

Intermediate 37b

NMR (DMSO) δ (ppm): 7.90 (s, 1H); 7.67 (s, 2H); 7.4-7.27 (m, 6H); 6.95 (dd, 1H); 6.80 (m, 1H); 5,74 (q, 1H); 4.60-4.40 (dd, 2H); 4.50 (m, 1H); 3.79 (m, 3H); 3.00 (m, 3H); 2.87 (s, 3H); 2.29 (s, 3H); 1.46 (d, 3H).

Intermediate 38
4-{[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereoisomer 1) (38a)

4-{[1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-carbamoyl}-3-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid 1-(S)-phenyl-ethyl ester (diastereoisomer 2) (38b)

To a solution of 1,1'Carbonyldiimidazole (0.163 g) in CH_2Cl_2 (5ml) (R)-sec-Phenethyl alcohol (0.122g) was added and the mixture was stirred at room temperature for 30 min. Then a solution of 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide (0.250g) in CH_3CN (5ml) was added and the mixture was refluxed for 4 hr. The mixture was cooled and ethyl acetate was added. The organic phase was washed with HCl 1N (2 X 50 ml) and brine, dried with Na_2SO_4 and concentrated to give the crude mixture of diastereoisomers which were separated by flash chromatography (silica gel, 8:2 cHex/EtOAc) to obtain the title compound 38a (diastereomer 1) (0.08g) and the title compound 38b (diastereomer 2)(0.08g).

Intermediate 38a: NMR ($CDCl_3$) δ (ppm) 7.74 (s, 1H); 7.52 (s, 2H); 7.40-7.24 (m, 5H); 7.18 (m, 1H); 6.87 (m, 1H); 6.80 (m, 1H); 5.86 (q, 1H); 5.57 (q, 1H); 4.7-4.46 (m, 1H); 3.98 (m, 2H); 3.44-2.96 (m, 4H); 2.77 (s, 3H); 2.36 (s, 3H); 1.54 (m, 6H).

Intermediate 38b NMR ($CDCl_3$) δ (ppm) 7.74 (s, 1H); 7.53 (s, 2H); 7.40-7.26 (m, 5H); 7.16 (m, 1H); 6.87 (m, 1H); 6.78 (m, 1H); 5.86 (q, 1H); 5.57 (m, 1H); 4.62 (m, 1H); 4.04 (m, 1H); 3.84 (m, 1H): 3.50-3.04 (m, 4H); 2.76 (s, 3H); 2.41 (s, 3H); 1.56 (m, 6H).

Intermediate 39

(+)3-(4-Fluoro-2-methyl-phenyl)--piperazin-2-one.

To a suspension of Intermediate 25 (35g) in AcOEt (900ml), L(+)-Mandelic Acid (27.3g) was added. The suspension was stirred at r.t for 1 hr then at 3-5°C for 2 hr filtered and dried under vacuum at r.t to obtain crude L(+)-mandelate 3-(4-Fluoro-2-methyl-phenyl)-piperazin-2-one (37g) which was suspended in Ethyl Acetate (370ml) and heating to reflux till complete solubilisation then cooled to room temperature and stirred for further 2 hours, filtered and washed with of Ethyl Acetate (150ml) dried under vacuum obtaining (+) L-mandelate 3-(4-Fluoro-phenyl)-5,6 dihydro-1H-pyrazin-2-one (30.4g) as white solid. (+) L-mandelate 3-(4-Fluoro-phenyl)-5,6 dihydro-1H-pyrazin-2-one (30.4g) was suspended in Ethyl Acetate (300ml) and treated with NaOH (0.73M 155ml) saturated with NaCl. The organic phase was then washed with water (90ml).

The aqueous phase was counter-extracted 4 times with ethyl acetate (90ml). The combined organic phase (1800ml) was dried on 10g of Na_2SO_4 and concentrated under vacuum obtaining the title compound (25.04g) as white foam.

HPLC: Chiralcel OJ (4.6X250mm) from Daicel; Mobile Phase:n-Hxane/Ethanol 80/20 v/v;Flow:1 mL/min; Detector:UV @ 265nm (or 210 nm for higher signals);Dissolutin phase:n-Hxane/Ethanol 80/20 v/v; Sample Concentration 1 mg/ml;Injection:5uL;Retention times: 2:8.4 min.

[α]D(solvent $CHCl_3$, Source : Na ; Cell volume [ml] : 1; Cell pathlength [dm]:1; Cell temperature [°C]:20; Wavelength [nm] : 589; Conc. sample [% p/v] :1.17)=+17.9.

Intermediate 40

2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amide.(diastereoisomer 1)(40a)

2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid [1-(3,5-bis-trifluor methyl-phenyl)-ethyl]-methyl-amide.(diast reoisomer 2)(40b)

To a solution of intermediate 39 (12.1g) in anhydrous CH_2Cl_2 (270ml), Et_3N (16.4ml) was added. The solution was cooled down to 0°C and a solution of triphosgene (7.3g) in anh. CH_2Cl_2 (60ml) was added drop-wise over 40 min. The reaction mixture was stirred at 0°C for 4 hr and was brought back to r.t.. iPr_2NEt (20.2ml) was then added, followed by a solution of [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl-amine (23.6g) in CH_3CN (300ml) and an additional 300ml of CH_3CN. The reaction mixture was warmed up to 95°C (oil bath T°C) without a water condensor to evaporate the CH_2Cl_2. When the intern temperature had reached 70°C, the flask was equipped with a water condenser, and the reaction mixture was heated at 70°C for an additional 2 hr (4 hr total). It was then brought back to r.t. and the solvent was evaporated. The residue was partitioned between CH_2Cl_2/2% HCl and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated to give a crude mixture of title compounds which were purified by flash chromatography (silica gel, EtOAc/cyclohexane 8/2) to obtain the tiltle compounds 40a (8.8g) and 40 b (9.0g) as white foams.

Intermediate 40a

NMR (^{1}H, DMSO-d_6): δ 8.16 (s, 1H), 7.98 (s, 2H), 7.19 (dd, 1H), 6.97 (dd, 1H), 6.87 (td, 1H), 5.34 (s, 1H), 5.14 (q, 1H), 3.45-3.2 (m, 4H), 2.53 (s, 3H), 2.27 (s, 3H), 1.56 (d, 3H).

Intermediate 40b

NMR (^{1}H, DMSO-d_6): δ 8.16 (s, 1H), 7.95 (s, 2H), 7.19 (dd, 1H), 6.98 (dd, 1H), 6.90 (td, 1H), 5.29 (q, 1H), 5.28 (s, 1H), 3.45-3.15 (m, 4H), 2.66 (s, 3H), 2.27 (s, 3H), 1.52 (d, 3H).

Intermediate 41

4-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of example 8 (0.05g) in anhydrous DMF (1ml), under N_2, at room temperature, were added triethylamine (40 µl) and N-(2-bromoethyl)-phthalimid (28mg). The reaction mixture was stirred at 80°C for 5 hr and was then cooled down to room temperature. It was poured in sat.aq. NaCl and the phases were separated. The organic

layer was washed with sat. aq. NaCl (2x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography to give the title compound (0.25g) as a yellow oil.

NMR (DMSO) δ (ppm) 7.94 (s, 1H), 7.80-7.90 (m, 4H), 7.67 (s, 2H), 7.33 (m, 1H), 6.91 (dd, 1H), 6.45 (td, 1H), 4.60 (d, 1H), 4.34 (m, 2H), 3.80 (m, 1H), 3.64 (m, 1H), 3.18 (m, 1H), 2.82 (s, 3H), 2.79 (m, 1H), 2.80 (m, 1H), 2.66 (m, 1H), 2.60 (m, 2H), 2.46 (m, 1H), 2.26 (m, 1H), 2.27 (s, 3H).
IR (Nujol) (cm^{-1}) 1650 – 1773.
MS (*m/z*) 651 [MH], 673 $[M+Na]^+$.

Intermediate 42
1-(4-Fluoro-2-methyl-phenyl)-propane-1,2-dione

1) To a suspension of magnesium turnings (283mg) in anh. THF (3 mL), at r.t., under N_2, was added a small crystal of I_2, followed by 10% of a solution of 1-bromo-4-fluoro-2-methyl-benzene (2.0g) in anhydrous . THF (8 mL). The suspension was heated gently (heat gun) until the brown colour disappeared. The rest of the bromide solution was added drop-wise, maintaining the reaction mixture warm (50-60°C) with an oil bath. After the addition was complete (15 min) the suspension was stirred at 70°C until the magnesium turnings had almost completely reacted (2 hr). The new brown solution was used in the next step.
2) A solution of LiBr (2.26g) in anh. THF (26 mL) was added drop-wise a suspension of CuBr (1.82 g) in anh. THF (26 mL). The reaction mixture was stirred at r.t. for 1 hr. The reaction mixture was then brought at -78°C and the Grignard solution prepared above was added dropwise followed by pyruvyl chloride (1.13g). The reaction mixture was stirred at -78°C for 2 hr. The THF was evaporated and the residue was taken up in EtOAc. The organic layer was washed with sat.aq. NH_4Cl (2x) and dried over Na_2SO_4. The solids were filtered and the solvent evaporated to give a crude oil, which was purified by flash chromatography. The title compound was obtained as a yellow oil (0.58g).
NMR ($CDCl_3$) δ (ppm) .7.68 (m, 1H), 6.98 (m, 2H), 2.56-2.52 (2s, 6H).
IR (Film) (cm^{-1}) 1712, 1674.

Intermediat 43

5-(4-Fluoro-2-methyl-phenyl)-6-methyl-2,3-dihydro-pyrazin

To a solution of intermediate 42 (0.58g) and ethylene diamine (0.22 mL) in toluene (13ml), at r.t., under N_2, was added anh. Na_2SO_4 (2g). The reaction mixture was heated at reflux for 6 hr. It was then cooled down to r.t. and filtered. The solids were rinsed with CH_2Cl_2. The solvent was evaporated and the crude oil was purified by flash chromatography. The title compound was obtained as an orange oil (0.44g).

NMR ($CDCl_3$) δ (ppm) 7.18 (m, 1H), 7.0-6.9 (m, 2H), 3.6-3.45 (2m, 4H), 2.20 (s, 3H), 1.88 (t, 3H).

IR (Film) (cm^{-1}) 1612, 1530.

MS (*m/z*) 204 $[M]^+$.

Intermediate 44

2-Methyl-3-phenyl-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 43 (554mg) in anh. MeOH (11ml), under N_2, at r.t., was added Pd/C 10% (110mg) and the reaction mixture was placed under an H_2 atmosphere for 2 hr. The catalyst was then filtered (filter paper) and rinsed with EtOAc. The solvent was evaporated and the residue dried under vacuum. 2-(4-Fluoro-2-methyl-phenyl)-3-methyl piperazine was obtained as a yellow oil (565mg) and was dissolvedin anh. CH_2Cl_2 (27ml), at -5°C, under N_2. To this solution were added Et_3N (549 µL) and CBZ-Cl (426 µL). The solution was stirred at -5°C for 2 hr. It was then poured in sat.aq. $NaHCO_3/CH_2Cl_2$ and the phases were separated. The aqueous layer was exptracted with CH_2Cl_2 (1x) and the combined organic extracts were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography. The title compound was obtained as a yellow oil (111mg).

NMR ($CDCl_3$) δ (ppm) 7.45-7.36 (m, 6H), 6.86 (m, 2H), 5.17 (m, 2H), 4.48-4.36 (m, 1H), 4.09-4.04 (2d, 1H), 4.05-3.94 (2bd, 1H), 3.25-2.88 (m, 3H), 2.40 + 2.28 (2s, 3H), 0.97 + 0.96 (2d, 3H).

IR (Film) (cm^{-1}) 1688.

MS (*m/z*) 343 $[MH]^+$.

Intermediate 45

4-[(3,5-Bis-trifluoromethyl-benzyl)-methyl-carbamoyl]-3-(4-fluoro-2-methyl-phenyl)-2-methyl-piperazine-1-carboxylic acid benzyl ester

To a solution of intermediate 44 (358mg) in anh. CH_2Cl_2 (15ml), at 0°C, under N_2, was added triethylamine (292 µL). To this solution was added a solution of triphosgene (140 mg) in anh. CH_2Cl_2 (6ml). The reaction mixture was stirred at 0°C for 2 hr.

To this solution were added iPr_2NEt (181 µL) and N-methyl-bis(trifluoromethyl)benzylamine hydrochloride (370mg). The solution was stirred at r.t. for 18 hr. It was then diluted with CH_2Cl_2, washed with 10% citric acid (1x) and dried over Na_2SO_4. The solids were filtered, the solvent was evaporated and the crude oil purified by flash chromatography. The title compound was obtained (545mg) as a white foamy solid.

NMR ($CDCl_3$) δ (ppm) 7.76 (s, 1H), 7.50 (s, 2H), 7.34-7.30 (m, 5H), 7.00 (m, 1H), 6.85 (m, 1H), 6.76 (m, 1H), 5.2-5.1 (dd, 2H), 4.75 (d, 1H), 4.30 (d, 1H), 4.65 (m, 1H), 4.35 (m, 1H), 4.00 (m, 1H), 3.54-3.40 (m, 2H), 3.1 (m, 1H), 3.06 (s, 3H), 2.38 (s, 3H), 1.05 (d, 3H).

IR (Film) (cm^{-1}) 3437, 1705, 1664.

MS (*m/z*) 626 $[MH]^+$.

Intermediate 46

3-(2-Methyl-4-fluoro-phenyl)-5-Methyl-5,6 dihydro-1H-pyrazin-2-one

under inert atmosphere Intermediate 23 (0.2g) was dissolved in dry toluene (5ml), then 1,2 diamino propane (0.102ml) was added drop-wise followed by Na_2SO_4 (0.2g) and the reaction mixture was refluxed for 2 hr; the solids were filtered off and the crude product obtained after evaporation of the solvent was purified by flash chromatography affording the title compound in a mixture with 3-(2-Methyl-4-fluoro-phenyl)-6-Methyl-5,6 dihydro-1H-pyrazin-2-one (0.200g).

^{1}H-NMR (DMSO) δ (ppm) 8.42 (bs, 1H), 7.24 (m, 1H), 7.02 (m, 2H), 3.85 (m, 1H), 3.40 (dt, 1H), 3.13 (t, 1H), 2.18 (s, 3H), 1.25 (d, 3H).

IR (Nujol) (cm^{-1}) 3450, 1682, 1614. MS (*m/z*) 221 $[MH]^+$.

Interm diat 47

3-(2-M thyl-4-fluoro-phenyl)-5-M thyl-piperazin-2-one (mixture of syn enantiomers)

Intermediate 46 (0.180g) was dissolved in MeOH (4ml) and Pd/C 10% (36mg) was added. After 2 hr the reduction was complete. The reaction mixture was filtered on a celite pad, the solvent was removed under reduced pressure and the crude product purified by flash-chromatography, affording a 9:1 mixture of the title compound and the anti enatiomers (0.110g).

^{1}H-NMR (DMSO) δ (ppm) 7.88 (s, 1H), 7.07-6.92 (m, 3H), 4.48 (s, 1H), 3.3 (m, 1H), 2.91 (m, 2H), 2.65 (bs, 1H), 2.34 (s, 3H), 0.95 (d, 3H).

IR (Nujol) (cm^{-1}) 3441, 3285, 1675.

MS (*m/z*): 223 $[MH]^+$.

Intermediate 48

2-(2-Methyl-4-fluoro-phenyl)-3-oxo-piperazine-6-Methyl-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; mixture of syn enantiomers

To a solution of intermediate 47 (0.105g) and triethylamine (0.197ml) in dry CH_2Cl_2 (5ml) was added drop-wise, at 0°C, a solution of triphosgene (0.056g) in dry CH_2Cl_2 (3ml) under inert atmosphere. The temperature was maintained at 0°C for 3 hr, before the addition of diisopropilethylamine (0.3ml) followed by 3,5-bistrifluoromethyl-methyl-amine hydrochloride (0.166g). The reaction mixture was stirred at room temperature overnight before being diluted with CH_2Cl_2 and washed with a 1N solution of HCl, H_2O and brine in sequence. The organic phase was dried on Na_2SO_4 and the crude product obtained after evaporation of the solvent was purified by flash column chromatography affording the title compound as a foam (0.085g).

^{1}H NMR (DMSO) δ (ppm) 8.08 (bt, 1H), 7.95 (s, 1H), 7.63 (s, 2H), 7.13 (t, 1H), 6.87 (d, 1H), 6.79 (t, 1H), 5.21 (s, 1H), 4.51 (dd, 2H), 3.64 (m, 1H), 3.30 (m,1H), 3.18 (m, 1H), 2.77 (s, 3H), 2.25 (s, 3H), 1.20 (d, 3H).

IR (Nujol) (cm^{-1}) 1675.

MS (*m/z*): 506 $[MH]^+$.

Example 1

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide; hydrochloride

A solution of intermediate 13 (0.05g) in EtOH (10ml) was hydrogenated at atmospheric pressure for 3 hr, in the presence of 10% Pd/C (10mg) as catalyst. The catalyst was filtered off and the solvent was evaporated. The crude residue dissolved in diethyl ether and then a 1M sol. of HCl in diethyl ether (0.1ml) was added. The formed precipitate was filtered and washed with diethyl ether to obtain the title compound (0.02g) as a white powder.

m.p. > 220°C

NMR (DMSO) δ (ppm) 9.33 (bm, 1H), 9.18 (bm, 1H), 7.96 (s, 1H), 7.59 (s, 2H), 7.33 (dd, 1H), 6.99 (d, 1H), 6.85 (t, 1H), 4.63 (d, 1H), 4.53 (d, 1H), 4.37 (d, 1H), 3.52 (d, 1H), 3.4-3.2 (m, 2H), 3.25 (m, 1H), 3.04 (t, 1H), 3.0-2.8 (m, 1H), 2.93 (s, 3H), 2.38 (s, 3H).

IR (Nujol) (cm^{-1}) 3200, 1659

MS (*m/z*) 478 $[M-Cl]^+$

Example 2

2-(3-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride

To a solution of intermediate 14 (0.353g) in anh. EtOH (5.7 mL), at r.t., under N_2, Pd/C 10% (175mg, 50% wt) was added. The black suspension was placed under an atmosphere of H_2 and was stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et_2O was then added (1.13 mL). The solvent was evaporated and the oil obtained was triturated with Et_2O. The solid was filtered, rinsed with Et_2O and dried under vacuum. The title compound was obtained as a grey solid (104mg).

m.p. 77-80°C

NMR ($CDCl_3$): δ (ppm) 8.95 (bs, 2H), 7.97 (s, 1H), 7.75 (s, 1H), 7.22-7.08 (m, 4H), 4.58-4.41 (2d, 2H), 4.50 (dd, 1H), 3.44 (m, 1H), 3.4-3.1 (m, 5H), 2.84 (s, 3H), 2.80 (m, 1H), 1.12 (d, 3H), 1.07 (d, 3H).

IR (Nujol) (cm^{-1}) 3437, 1653

MS (*m/z*) 488 $[M-Cl]^+$

Example 3

2-(2-Isopropyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride.

To a solution of intermediate 15 (0.108g) in anh. EtOH (2.0 mL), at r.t., under N_2, Pd/C 10% (20mg, 20% wt) was added. The black suspension was placed under an atmosphere of H_2 and was stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et_2O was then added (350 µL). The solvent was evaporated and the oil obtained was triturated with Et_2O. The solid was filtered, rinsed with Et_2O and dried under vacuum. The title compound was obtained as a brown solid (29mg).

m.p. 108-110°C

NMR ($CDCl_3$): δ (ppm) 9.15 (bd, 1H), 8.92 (bd, 1H), 7.97 (s, 1H), 7.66 (s, 2H), 7.30 (m, 1H), 7.27 (m, 1H), 7.19 (dt, 1H), 7.03 (dt, 1H), 4.69 (dd, 1H), 4.55 (2d, 2H), 3.53 (m, 1H), 3.39 (m, 3H), 3.19 (bd, 1H), 3.04 (dt, 1H), 2.92 (m, 4H), 1.24 (d, 3H), 1.20 (d, 3H).

IR (Nujol) (cm^{-1}) 3441, 1662.

MS (*m/z*) 489 $[M\text{-}Cl]^+$.

Example 4

2-(4-Fluoro-3-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride.

To a solution of intermediate 16 (0.226g) in anh. EtOH (3.7 mL), at r.t., under N_2, Pd/C 10% (23 mg, 10% wt) was added. The black suspension was placed under an atmosphere of H_2 and stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et_2O was then added (740 µL). The solvent was evaporated and the oil obtained was triturated with Et_2O. The solid was filtered, rinsed with Et_2O and dried under vacuum. The title compound was obtained as a white solid (112mg).

m.p. 70-72°C

NMR ($CDCl_3$): δ (ppm) 9.08 (m, 2H), 7.97 (s, 1H), 7.67 (s, 2H), 7.19 (m, 1H), 7.14 (m, 1H), 7.01 (t, 1H), 4.59 (d, 1H), 4.43 (m, 1H), 4.40 (d, 1H), 3.1-3.5 (m, 6H), 2.92 (s, 3H), 2.14 (s, 3H).

IR (Nujol) (cm^{-1}) 3406, 1653

MS (*m/z*) 478 $[M\text{-}Cl]^+$

Example 5

2-(2,4-Difluoro-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride

To a solution of intermediate 17 (0.134g) in anh. EtOH (2.0 mL), at r.t., under N_2, Pd/C 10% (27mg, 20% wt) was added. The black suspension was placed under an atmosphere of H_2 and was stirred for 3 hr. The catalyst was then filtered on Celite and the Celite cake was rinsed with EtOH. HCl 1.0M/Et_2O was then added (436 µL). The solvent was evaporated and the oil obtained was triturated with Et_2O. The solid was filtered, rinsed with Et_2O and dried under vacuum. The title compound was obtained as a yellow solid (112mg).

m.p. 220-230°C

NMR ($CDCl_3$): δ (ppm) 9.08-9.3 (m, 2H), 7.97 (s, 1H), 7.62 (s, 2H), 7.44 (m, 1H), 7.18 (m, 1H), 6.95 (m, 1H), 4.65 (m ,1H), 4.3-4.65 (dd, 2H), 3.2-3.6 (m, 4H), 3.07 (m, 2H), 2.92 (s, 3H).

IR (Nujol) (cm^{-1}) 3400, 1656

MS (*m/z*) 482 $[M-Cl]^+$.

Example 6

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-amide; hydrochloride

A solution of intermediate 18 (0.086g) in EtOH (10ml) was hydrogenated at atmospheric pressure for 2 hr, in the presence of 10% Pd/C (20mg) as catalyst. The catalyst was filtered off and the solvent was evaporated. The crude residue dissolved in diethyl ether and then a 1M sol. of HCl in diethyl ether (0.1ml) was added. The solvent was evaporated to obtain the title compound (0.05g) as a white solid.

NMR (DMSO) δ (ppm) 9.06 (m, 1H), 8.88 (m, 1H), 7.91 (s, 1H), 7.77 (s, 2H), 7.42 (t, 1H), 7.22 (dd, 1H), 7.03 (m, 1H), 6.94 (t, 1H), 5.22 (t, 1H), 4.34 (m, 2H), 3.98 (m, 1H), 3.64 (m, 1H), 3.4-3.2 (m, 2H), 3.22 (m, 2H), 2.32 (s, 3H).

IR (Nujol) (cm^{-1}) 3360, 1645

MS (*m/z*) 464 $[M-Cl]^+$.

Exampl 7

(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride

A solution of intermediate 20a (0.120g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in the presence of 10% Pd/C (25mg). Then the catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.3ml) was added. Then the precipitate was filtered and washed with diethyl ether to obtain the title compound (0.057g) as a white solid.

m.p.>220°C

NMR (DMSO) δ (ppm) 9.11 (m, 1H); 8.83 (m, 1H); 7.96 (s, 1H); 7.59 (s, 2H); 7.34 (dd, 1H); 6.94 (dd, 1H); 6.86 (m, 1H); 4.65-4.35 (dd, 2H); 4.49 (m, 1H); 3.54 (m, 1H); 3.44-3.01(m, 4H); 2.93 (s, 3H); 2.90 (m, 1H); 2.38 (s, 3H).

MS (*m/z*) 479 $[MH\text{-}Cl]^+$

$[\alpha]^D_{20}$ = +69.5 C = 0.27(g/100ml) $CHCl_3$

Example 8

Method A

(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide hydrochloride

A solution of intermediate 20b (0.110g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in the presence of 10% Pd/C (25mg). Then the catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.3ml) was added. Then the precipitate was filtered and washed with diethyl ether to obtain the title compound (0.045g) as a white solid.

Method B

(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide; hydrochloride

A solution of intermediate 37a (0.24g) in EtOH (4ml) was hydrogenated at atmospheric pressure for 3 hr, in the presence of 10% Pd/C (73mg) as catalyst. The catalyst was filtered off and the solvent was evaporated. The crude residue dissolv d in diethyl ether and then a 1M sol. of HCl in diethyl ether (0.58ml) was added. The formed precipitate was filtered and

washed with diethyl ether to obtain the title compound (0.04g) as a white powder.

Method C

To Intermediate 39 (2.37g) triethylamine (3.15ml) in dry CH_2Cl_2 (57ml) was added drop-wise, at 0°C. Then a solution of triphosgene (1.502g) in dry CH_2Cl_2 (12ml) under inert atmosphere was added. The temperature was maintained at 0°C for 3 hr, before the addition of diisopropilethylamine (4ml) followed by 3,5-bis-trifluoromethylbenzyl-N-methyl amine (4.62g) in acetonitrile (142ml). The reaction mixture was heated to reflux for 3 hr then cooled to room temperature diluted with CH_2Cl_2 (25ml) and washed with a 1N solution of HCl (25ml), H_2O (25ml) and brine (25ml) in sequence. The organic phase was dried on Na_2SO_4 (2g) and the crude product obtained after evaporation of the solvent was purified by flash column chromatography (from Ethyl Acetate/Cyclohexane 4/1 to pure Ethyl Acetate) to give 2-(4-Fluoro-2-methyl-phenyl)-3-oxo-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide as a foam (1.79g).

This compound was reduced with BH_3.THF (17.6ml) following the standard procedure (4 hr reflux in 10ml of THF, then work-up with 6ml of HCl 37% and subsequent neutralisation with 5g of solid $NaHCO_3$) to give the title compound (1.16g).

m.p.>220°C

NMR (DMSO) δ (ppm) 9.11 (m, 1H); 8.83 (m, 1H); 7.96 (s, 1H); 7.59 (s, 2H); 7.34 (dd, 1H); 6.94 (dd, 1H); 6.86 (m, 1H); 4.65-4.35 (dd, 2H); 4.49 (m, 1H); 3.54 (m, 1H); 3.44-3.01(m, 4H); 2.93 (s, 3H); 2.90 (m, 1H); 2.38 (s, 3H).

MS (*m/z*) 479 $[MH-Cl]^+$

$[\alpha]^D_{20}$ = -72.6 C = 0.27(g/100ml) $CHCl_3$

Example 9

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide;hydrochloride (mixture of the enantiomers A,B)

A solution of intermediate 22a (0.05g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 1 ½ hr, in the presence of 10% Pd/C (15mg). Then the catalyst was filt red off and the solvent was evaporated. Th

crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. Then the precipitate was filtered and washed with diethyl ether to obtain the title compound (0.025g) as a white powder.

NMR ($CDCl_3$) δ (ppm) 10.2 (b, 1H); 7.78 (s, 1H); 7.54 (s, 2H); 7.13 (dd, 1H); 6.88 (dd, 1H); 6.82 (m, 1H); 5.48 (q, 1H); 4.57 (m, 1H); 3.6-3.5 (m, 2H); 3.38 (m, 2H); 3.3-3.0 (m, 2H); 2.71 (s, 3H); 2.48 (s, 3H); 1.44 (d, 3H).

IR($CDCl_3$) 1663

MS (*m/z*) 491 $[M-Cl]^+$

Example 10

2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; hydrochloride (mixture of the enantiomers C,D)

A solution of intermediate 22b (0.05g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 1 ½ hr, in the presence of 10% Pd/C (15mg). Then the catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. Then the precipitate was filtered and washed with diethyl ether to the title compound (0.057g) as a white powder.

NMR ($CDCl_3$) δ (ppm) 10.2 (b, 1H); 7.74 (s, 1H); 7.41 (s, 2H); 7.10 (m, 1H); 6.88 (m, 1H); 6.80 (m, 1H); 5.58 (q, 1H); 4.85 (m, 1H); 3.7-2.9 (m, 6H); 2.80 (s, 3H); 2.49 (s, 3H); 1.44 (d, 3H).

IR ($CDCl_3$) 1662

MS (*m/z*) 491 $[M-Cl]^+$

Example 11

2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide

To a solution of intermediate 32 (813mg) in anh. THF (6.6 mL), at r.t., under N_2, BH_3·THF 1M/THF (9.9 mL) was added. The solution was heated at reflux for 3 hr. It was then brought back to r.t. and 1N HCl (4 mL) was added slowly in order to destroy the borane complexes. The reaction mixture was stirred at r.t. for 18 hr. The THF was evaporated

and the aqueous phase was basified with 10% NaOH. It was then extracted with EtOAc (3x). The combined organic extracts were dried over Na_2SO_4, the solids were filtered and the solvent evaporated. The title compound was used as such in the next step (790mg).

NMR ($CDCl_3$): δ (ppm) 7.77 (s, 1H), 7.49 (s, 2H), 7.33 (m, 1H), 6.86 (m, 1H), 6.82 (m, 1H), 4.65-4.46 (2d (AB), 2H), 4.46 (m, 1H), 3.40-2.85 (m, 6H), 2.97 (s, 3H), 2.66 (s, 3H).

IR ($CDCl_3$; cm^{-1}): 1653.

MS (*m/z*): 478 $[MH]^+$

Example 12

2-(4-Fluoro-phenyl)- piperazine-1-carboxylic acid (3,4-bis-trifluoromethyl-benzyl)-methyl-amide; hydrochloride.

Intermediate 33 (0.180g) was dissolved in dry THF (8ml) under inert atmosphere; BH_3.THF complex (1.88ml) was added very carefully and the reaction mixture was refluxed 3 hr. After completion of the reduction HCl 37% was added (3ml) and the reaction mixture was refluxed 2 hr. THF was removed under reduced pressure, water was added (3ml) and the aqueous solution was basified by means of Na_2CO_3, extracted with CH_2Cl_2, washed with brine and dried on Na_2SO_4. The crude product was purified by flash chromatography (silica gel, 8:2 EtOAc/MeOH) affording the free amine which was treated with a 1M solution of HCl in Et_2O (0.3ml) to yield the title compound (0.05g) as a white solid.

mp> 200°C

NMR (DMSO) δ (ppm): 9.08 (bs, 2H), 7.97 (s, 1H), 7.66 (s, 2H), 7.35 (m, 2H), 7.10 (m, 2H), 4.60 (d, 1H), 4.46 (dd, 1H), 4.39 (d, 1H), 3.50-3.10 (m, 6H), 2.92 (s, 3H).

IR (Nujol) (cm^{-1}) 3437, 1653

MS: 464 $[M-Cl]^+$.

Example 13

2-Phenyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl- amide; hydrochloride.

To a stirred solution of intermediate 34 (0.382g) in THF (10ml) a 1M solution of BH_3 in THF (1.66ml) was added. The mixture was th n reflux d for 3 hr. The t mperature was then cooled, and the reaction was quenched with a solution of HCl 37% (5ml) and stirred at room

temperature overnight. The solution was then basified with NaOH and the product was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated under reduced pressure to give an oil. The oil was then dissolved in Et_2O and a 1M solution of HCl in Et_2O (1,6ml) was added. After a few minutes the solution was concentrated, and the product was triturated from petroleum ether to give the title compound (0.300g) as a solid.
NMR($CDCl_3$): δ (ppm): 10.15(b, 2H); 7.75(s, 1H); 7.44(s, 2H); 7.3(m, 5H); 4.80-4.34(m, 3H); 3.80-3.00(m, 6H); 2.93(s, 3H)
MS (m/z):446 $[M-Cl]^+$.

Example 14
2-(2,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro methyl-benzyl)-methyl-amide hydrochloride.

To a solution of intermediate 35 (0.22g) in THF (15ml) a 1M solution of borane in THF (1.2ml) was added and the reaction mixture was stirred at reflux for 3 hr, then cooled to r.t. 37% HCl (3ml) was added drop-wise and the reaction mixture stirred for 3 hr. The solvent was evaporated and the crude residue was diluted with ethyl acetate and washed with a saturated solution of $NaHCO_3$ and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product. The latter was dissolved in diethyl ether (2ml), then a 1M sol of HCl in diethyl ether (1ml) was added. The obtained solution was added drop-wise in petroleum (30ml) and the formed precipitate was filtered to obtain the title compound (0.06g, white solid).
NMR (DMSO) δ (ppm) 9.25, 9.15 (m+m, 2H), 7.98 (m, 1H), 7.64 (s, 2H), 7.60 (d, 1H), 7.45 (d, 1H), 7.29 (dd, 1H), 4.78 (dd, 1H), 4.63 (d, 1H), 4.35 (d, 1H), 3.59 (d, 1H), 3.40-3.25 (m, 3H), 3.07 (t, 3H), 2.95, 2.93 (s+m, 4H).
IR (Nujol) (cm^{-1}) 3442, 1654
MS (*m/z*) 515 $[M-Cl]^+$.

Example 15
2-(3,4-dichloro-phenyl)-piperazine-1-carboxylic acid (3,5-bistrifluoro m thyl-b nzyl)-m thyl-amide; hydrochloride.

To a solution of intermediate 36 (0.13g) in THF (20ml) a 1M solution of borane in THF (1.96ml) was added and the reaction mixture was stirred

at reflux for 3 hr, then cooled to r.t. 37% HCl (5ml) was added drop-wise and the reaction mixture was stirred for 3 hr. The solvent was evaporated and the crude residue was diluted with ethyl acetate and washed with a saturated solution of $NaHCO_3$ and brine. The organic phase was next dried with Na_2SO_4 and concentrated to give the crude product. The latter was dissolved in diethyl ether (2ml), then a 1M sol of HCl in diethyl ether (1ml) was added. The obtained solution was added drop-wise in petroleum (30ml) and the formed precipitate was filtered to obtain the title compound (0.016g; white solid).

NMR (DMSO) δ (ppm) 8.99 (broad, 2H), 7.98 (s, 1H), 7.70 (s, 2H), 7.56 (d+d, 2H), 7.31 (dd, 1H), 4.58 (d, 1H), 4.50 (d, 1H), 4.41 (d, 1H), 3.5-3.1 (m, 4H), 2.93 (s, 3H).

IR (Nujol) (cm^{-1}) 3436, 1653

MS (*m/z*) 515 $[M-Cl]^+$.

Example 16

(-)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide; hydrochloride (Enantiomer A)

A solution of intermediate 38a (0.08g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in presence of 10% Pd/C (50mg). The catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. The precipitate was filtered and washed with diethyl ether to obtain the title compound (0.023g).

NMR ($CDCl_3$) δ (ppm) 10.5-10.0 (b, 2H); 7.74 (s, 1H); 7.41 (s, 2H); 7.09 (m, 1H); 6.88 (m, 1H); 6.80 (m, 1H); 5.58 (q, 1H); 4.85 (m, 1H); 3.80-3.00 (m, 6H); 2.80 (s, 3H); 2.49 (s, 3H); 1.53 (d, 3H).

MS (*m/z*) 492

$[\alpha]^D_{20}$ = -164.9, 0.12(g/100ml) $CHCl_3$

Example 17

(+)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluorom thyl-phenyl) thyl]-methyl-amide; hydrochlorid (Enantiomer B)

A solution of intermediate 38 b (0.08g) in EtOH (5ml) was hydrogenated at atmospheric pressure for 4 hr, in presence of 10% Pd/C (50mg). The catalyst was filtered off and the solvent was evaporated. The crude product was dissolved in diethyl ether and then a solution 1M of HCl in diethyl ether (0.5ml) was added. The precipitate was filtered and washed with diethyl ether to obtain the title compound (0.020g).

NMR ($CDCl_3$) δ (ppm) 10.5-10.0 (b, 2H); 7.74 (s, 1H); 7.41 (s, 2H); 7.09 (m, 1H); 6.88 (m, 1H); 6.80 (m, 1H); 5.58 (q, 1H); 4.85 (m, 1H); 3.80-3.00 (m, 6H); 2.80 (s, 3H); 2.49 (s, 3H); 1.53 (d, 3H).

MS (*m/z*) 492

$[\alpha]^{D}_{20}$ = +207, 0.11 (g/100ml) $CHCl_3$

Example 18

2--(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl- amide; acetate salt (enantiomerC)

To a solution of intermediate 40a (8.8g) in dry THF (33ml) under N_2 BH_3.THF (1M solution in THF 87ml) was added and the reaction mixture was stirred at reflux for 3 hr, then cooled to r.t. and HCl (37%,30 ml) was added drop-wise maintaining the reaction mixture in an ice–bath. The reaction mixture was stirred at r.t. for 1 hr. Water was then added (70ml) and solid $NaHCO_3$ (35.2g) was added portionwise until a pH of 6.5.

The THF was evaporated and the aqueous phase was extracted with Et_2O (3x88ml). The combined organic phases were dried (Na_2SO_4), and evaporated to leave a colourless oil (7.37g).

This crude oil was purified by flash chromatography (silica gel EtOAc/Methanol 7/3). The product obtained was suspended in Et_2O (125ml) and washed with $NaHCO_3$ sat. (2x20ml). The clear combined organic phases were dried on Na_2SO_4 and evaporated to obtain the title compound as white foam (5.27gr).

NMR (^{1}H, DMSO-d_6): δ 7.98 (s, 1H), 7.70 (s, 2H), 7.87 (m, 1H), 6.91 (m, 1H), 6.77 (m, 1H), 5.29 (q, 1H), 4.23 (dd, 1H), 3.2-2.6 (m, 6H), 2.68 (s, 3H), 2.3 (s, 3H), 1.89 (s, 3H), 1.48 (d, 3H).

MS (m/z): 492 $[M\text{-}CH_3COO]^+$.

$[\alpha]^{D}$ = - 120.4°CSolvent (CHCl3); Source:Na; Cell volume [mL]: 1; Cell pathlength [dm]: 1; Cell temperature [°C]: 20; Wavelength [nm]: 589

Example 19

2-(4-Fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)-ethyl]-methyl- -amide; acetate salt (enantiomer A)

To a solution of intermediate 40b (2.57g) in dry THF (15.5ml), at 0°C, under N_2, was added BH_3·THF (1M solution in THF) then heated at reflux for 3 hr. It was then brought back to r.t. and HCl 37% (9ml) was added slowly maintaining the reaction mixture in an ice-bath. The reaction mixture was stirred at r.t. for 1 hr. Water was then added (20.5ml) and solid $NaHCO_3$ (10.3g) was added portionwise until a pH of 7.

The THF was evaporated and the aqueous phase was extracted with Et_2O (3x25.7ml). The combined organic phases were dried (Na_2SO_4), and evaporated to leave a yellow oil (2.34g). This crude oil was dissolved in Et_2O (35ml) and glacial AcOH (0.245ml) was added drop-wise. The mixture was stirred 2 hr at 0°C, then it was filtered, washed with Et_2O (10ml) and dried under vacuum to obtain the title compound as a white solid (1.349gr).

NMR (^{1}H, DMSO-d_6): δ 7.92 (s, 1H), 7.58 (s, 1H), 7.29 (m, 1H), 6.90 (m, 1H), 6.77 (m, 1H), 5.33 (q, 1H), 4.19 (m, 1H), 3.2-2.6 (m, 6H), 2.79 (s, 3H), 2.32 (s, 3H), 1.89 (s, 3H), 1.48 (d, 3H).

MS (m/z): 492 $[M\text{-}CH_3COO]^+$.

$[\alpha]^D$ = +2.2 °C

Solvent (CHCl3); Source:Na; Cell volume [mL]: 1; Cell pathlength [dm]: 1; Cell temperature [°C]: 20; Wavelength [nm]: 589

Example 20

4-(2-Amino-acetyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid(3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride

Example 8 (0.05g) was dissolved in dry DMF (2ml), diisopropylethylamine (0.019ml) was added and the solution thus obtained was added to a solution of N-(tert-butoxycarbonyl)glycine (0.0192g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.0214g) and 1-hydroxybenzotriazole (0.015g) in dry DMF (5ml). The r action mixture was stirred 18hr at room temperature, then dilut d with ethyl acetate

(30ml), washed with water (30ml), sodium bicarbonate (30ml) and brine (30ml). The separated organic layer was dried on sodium sulphate, filtered and evaporated and the crude was then chromatographed (silica gel, 100% EtOAc) to give a product (0.043g) which was dissolved in a 1M solution of HCl in diethylether (5ml), stirred 0.5 hr at room temperature and evaporated to obtain the title compound (0.046g) as a yellow foam.

NMR (DMSO) δ (ppm) 8.01 (bs, 3H), 7.88 (s, 1H), 7.67 (s, 2H), 7.33 (m, 1H), 6.95 (m, 1H), 6.83 (m, 1H), 4.60 (m, 1H), 4.60-4.42 (dd, 2H), 4.2-3.3 (m, 6H), 3.2 (m, 2H), 2.89 (s, 3H), 2.4 (s, 3H).

IR (Nujol) (cm^{-1}) 3410, 1660.

MS (*m/z*) 535 $[M-Cl]^+$.

Example 21

2-(4-fluoro-2-methyl-phenyl)-4-(piperidine-4-carbonyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride

Example 8 (0.05g) was dissolved in dry DMF (2ml), diisopropylethylamine (0.019ml) was added and the solution thus obtained was added to a solution of piperidine-1,4-dicarboxylic acid mono-tert-butyl ester (0.0192g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.025g) and 1-hydroxybenzotriazole (0.015g) in dry DMF (5ml). The reaction mixture was stirred 18 hr at room temperature, then diluted with ethyl acetate (30ml), washed with water (30ml), sodium bicarbonate (30ml) and brine (30ml). The separated organic layer was dried on sodium sulphate, filtered and evaporated. The crude was then chromatographed (silica gel, 9:1 EtOAc/MeOH) to give a product (0.040g) which was dissolved in a 1M solution of HCl in diethylether (5ml), stirred 0.5 hr at room temperature and evaporated to obtain the title compound (0.043g) as a yellow foam.

NMR (DMSO) δ (ppm) 8.71 (bs, 1H), 8.38 (bs, 1H), 7.86 (s, 1H), 7.66 (s, 2H), 7.31 (m, 1H), 6.95 (m, 1H), 6.83 (m, 1H), 4.55 (m, 1H), 4.60-4.43 (dd, 2H), 3.9-3.4 (m, 7H), 2.8-2.7 (m, 8H), 2.88 (s, 3H), 2.37 (s, 3H).

IR (Nujol) (cm^{-1}) 3401, 1639.

MS (*m/z*) 589 $[M-Cl]^+$.

Example 22

4-(2-Amino-ethyl)-2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, dihydrochloride salt

To a solution of intermediate 41 (25mg) in absolute EtOH (1mL), at room temperature, was added methylamine 8.03M/EtOH (48 µL). The reaction mixture was stirred at r.t. for 5 hr. The solvent was evaporated and the crude product purified by flash chromatography (silica gel, 90:5:5 EtOAc/MeOH/NH_4OH conc.). The fractions were collected and the solvent was evaporated. The residue was dissolved in Et_2O and HCl 1.0M/Et_2O (150 µL) was added. The yellow precipitate was filtered and dried to give the title compound (19mg) as a yellow solid.

NMR (DMSO) δ (ppm) 8.12 (bs, 2H), 7.90 (s, 1H), 7.62 (s, 2H), 7.33 (t, 1H), 6.95 (dd, 1H), 6.83 (td, 1H), 4.69 (m, 1H), 4.62 (d, 1H), 4.41 (d, 1H), 3.60-3.10 (m, 10H), 2.94 (s, 3H), 2.40 (s, 3H).

IR (Nujol) (cm^{-1}) 3433 – 3300, 1651.

MS (*m/z*) 521 $[M-2HCl+H]^+$.

Example 23

2-(4-Fluoro-2-methyl-phenyl)-3-methyl-piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride salt

To a solution of intermediate 45 (100mg) in anh. MeOH (3ml), under N_2, at room temperature, was added Pd/C 10% (20mg). The reaction mixture was placed under an H_2 atmosphere and stirred at room temperature for 2 hr. The catalyst was filtered on Celite, and the Celite cake was rinsed with EtOAc. The solvent was evaporated and the residue was dissolved in Et_2O. HCl 1.0N/Et_2O (240 µl) was added and the white precipitate was filtered and rinsed with Et_2O. The title compound was obtained (73mg) as a white solid.

NMR ($CDCl_3$) δ (ppm) 9.31 + 9.01 (m, 2H), 7.99 (s, 1H), 7.70 (s, 2H), 7.02 (m, 2H), 6.78 (m, 1H), 4.63 (d, 1H), 4.7-4.3 (dd, 2H), 3.66 (m, 1H), 3.5-2.9 (m, 4H), 3.05 (s, 3H), 2.34 (s, 3H), 1.09 (d, 3H).

IR (Film) (cm^{-1}) 1659.

MS (*m/z*) 692 $[MH-Cl]^+$.

Example 24

2-(2-M thyl-4-Flu ro-phenyl)-6-Methyl- piperazine-1-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide, hydrochloride salt.(mixture of syn enantiomers)

Intermediate 47 (0.080g) was dissolved in dry THF (5ml) under inert atmosphere; BH_3·THF complex (1.25ml) was added very carefully and the reaction mixture was refluxed for 3 hr. After completion of the reduction, HCl 37% was added (3ml) and the reaction mixture was refluxed for 2 hr. THF was removed under reduced pressure, water was added (3ml) and the aqueous solution was basified by means of Na_2CO_3, extracted with CH_2Cl_2, washed with brine and dried on Na_2SO_4. The crude product was purified by flash chromatography (silica gel, 8:2 EtOAc/MeOH) affording a product which was dissolved in Et_2O and treated with HCl 1.0M/Et_2O (0.3 mL) affording 0.03g of the title compound.

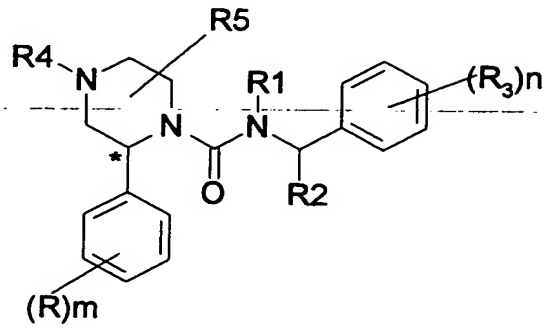
^{1}H-NMR (DMSO) δ (ppm) 9.12 (bs, 1H), 8.88 (bs, 1H), 7.93 (s, 1H), 7.56 (s, 2H), 7.37 (m, 1H), 6.74 (m, 2H), 4.71 (d,1H), 4.35 (dd,1H), 4.36-4.10 (bm, 1H), 3.35-2.9 (m, 5H), 2.99 (s, 3H), 2.28 (s, 3H), 1.05 (d, 3H).

MS (*m/z*) 492 $[M - Cl]^+$.

mp> 200 °C.

Claims

1. A compound of formula (I)



wherein

R represents a halogen atom or a C_{1-4} alkyl group;

R_1 represents hydrogen or a C_{1-4} alkyl group;

R_2 represents hydrogen or a C_{1-4} alkyl group;

R_3 represents a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, a trifluoromethoxy or a halogen group;

R_4 represents hydrogen, a $(CH_2)qR_7$ or a $(CH_2)rCO(CH_2)pR_7$ group;

R_5 represents hydrogen, a C_{1-4} alkyl or a COR_6 group;

R_6 represents hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R_7 represents hydrogen, hydroxy, a saturated 5-7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or NR_8R_9 wherein R_8 and R_9 represent independently hydrogen or C_{1-4} alkyl optionally substituted by a hydroxy, amino, by a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, by a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or saturated 5-7 membered heterocyclic or R_8 and R_9 together with the nitrogen atom to which th y are attached r present a saturated

5-7 membered heterocyclic group optionally containing an additional heteroatom selected from oxygen, sulphur or nitrogen;
m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; p or r iare zero or an integer from 1 to 4; q is an integer from 1 to 4 and pharmaceutically acceptable salts.

2. 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide (enantiomer C); and pharmaceutically acceptable salts and solvates thereof.

3. 2-(4-fluoro-2-methyl-phenyl)-piperazine-1-carboxylic acid [1-(3,5-bis-trifluoromethyl-phenyl)ethyl]-methyl-amide acetate salt. (enantiomer C).

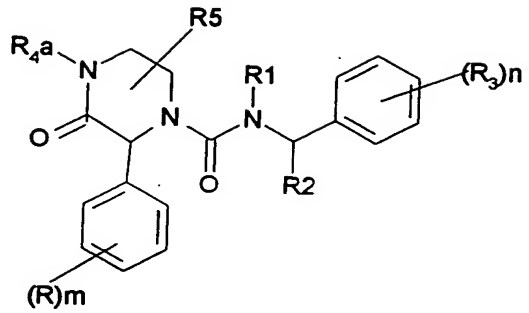
4. A compound as claimed in any of claims 1-3 for use in therapy.

5. The use of a compound as claimed in any of claims 1-3 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

6. A pharmaceutical composition comprising a compound as claimed in any of claims 1-3 in admixture with one or more physiologically acceptable carriers or excipients.

7. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound claimed in any claims 1 to 3.

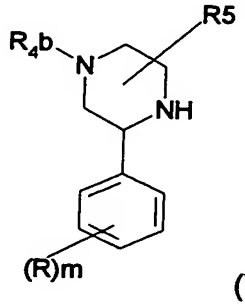
8. A process (A) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is hydrogen or a $(CH_2)qR_7$ group, provided that when R_5 is a C_{1-4} alkyl or a COR_6 group, R_5 is not in 3 position of the piperazine ring, which comprises reduction of a compound of formula (II), wherein R_{4a} is hydrogen or a suitable nitrogen protecting group or R_{4a} is a $(CH_2)qR_7$ group or protecting d rivatives thereof.



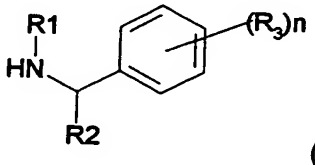
(II)

or

a process (B) for the preparation of a compound of formula (I) as claimed in claim 1, wherein R_4 is hydrogen or a $(CH_2)rCO(CH_2)pR_7$ group which comprises the reaction of a compound of formula (VIII), wherein R_{4b} represents a nitrogen protecting group or R_{4b} is $(CH_2)r$ $CO(CH_2)pR_7$ or a protecting group thereof with triphosgene and an organic base followed by addition of the amine (V)



(VIII),



(V)

followed where necessary or desired by one or more of the following step:

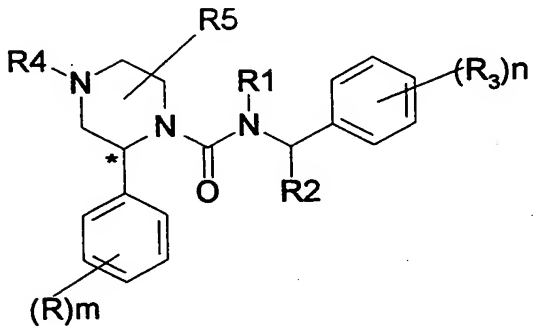
(i) removal of any protecting group;

(ii) isolation of the compound as salt thereof;

(iii) separation of a compound of formula (I) or derivative thereof into the enantiomers thereof.

Abstract

The present invention relates to piperazine derivatives of formula (I)



wherein

R represents a halogen atom or a C_{1-4} alkyl group;

R_1 represents hydrogen or a C_{1-4} alkyl group;

R_2 represents hydrogen or a C_{1-4} alkyl group;

R_3 represents a trifluoromethyl, a C_{1-4} alkyl, a C_{1-4} alkoxy, trifluoromethoxy or an halogen group;

R_4 represents hydrogen, a $(CH_2)qR_7$ or a $(CH_2)rCO(CH_2)pR_7$ group;

R_5 represents hydrogen, a C_{1-4} alkyl or a COR_6 group;

R_6 represents hydrogen, hydroxy, amino, methylamino, dimethylamino, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

R_7 represents hydrogen, hydroxy, a saturated 5-7 membered heterocyclic group, a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or NR_8R_9 wherein R_8 and R_9 represent independently hydrogen or a C_{1-4} alkyl group optionally substituted by a hydroxy, amino, by a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen, by a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms or saturated 5-7 memb r d heterocyclic or R_8 and R_9 together with the nitrogen atom to which they are attached r present a saturated

5-7 membered heterocyclic group optionally containing an additional heteroatom selected from oxygen, sulphur or nitrogen;
m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; p or r are zero or an integer from 1 to 4; q is an integer from 1 to 4 and pharmaceutically acceptable salts; to processes for their preparation and their use in the treatment of conditions mediated by tachykinins.